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APPLICATION NUMBER:

20-947

MEDICAL REVIEW(S)

CLINICAL REVIEW UPDATE

Application Type:	NDA
Submission Number	20947
Letter Date	February 4, 2009
Stamp Date	February 4, 2009
PDUFA Goal Date	August 4, 2009
Reviewer	Nick Olmos-Lau, M.D.
Team Leader (acting)	Jin Chen, MD
Division Deputy Director	Sharon Hertz, M.D.
Division Director	Bob A Rappaport, MD
Review Completion Date	June 2008
Established Name	Topical solution w/w 1.5% diclofenac sodium
(Proposed) Trade Name	PENNSAID
Therapeutic Class	Non-steroidal anti-inflammatory drug
Applicant	Dimethaid International Inc.
Priority Designation	S
Formulation	Topical solution (1.5% diclofenac sodium, 45.5% dimethyl sulfoxide, ——— propylene glycol, ——— glycerine, ——— ethyl alcohol———— purified water b(4)
Dosing Regimen	40 drops 4 times a day to the affected knee
Indication	osteoarthritis of the knee
Intended Population	primary osteoarthritis of the knee

INTRODUCTION

This submission is a complete response to an approvable (AE) letter issued on February 5, 2009. The proposed indication of this product is for the treatment of signs and symptoms of knee osteoarthritis (OA) at a dose of 40 drops qid. The product has a long regulatory history; however, at this point there are no outstanding clinical safety or efficacy concerns.

Pennsaid is a topical solution containing 1.5% w/w diclofenac sodium as the active ingredient and 45.5% dimethyl sulfoxide an active penetration enhancer. The other components of this preparation include —— propylene glycol, —— glycerine, —— ethyl alcohol —— and —— purified water. This formulation was developed for local, topical delivery of the non-steroidal anti-inflammatory drug diclofenac sodium, to joints affected by primary osteoarthritis (OA). b(4)

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that works as an inhibitor of the COX-1 and COX-2 isoforms of the cyclooxygenase (COX) enzyme. It has both anti-inflammatory and analgesic properties. Administration of diclofenac sodium may produce gastro-intestinal irritation and hemorrhage, hypertension, edema and deterioration of renal function. Abnormalities of liver transaminase and decreased hemoglobin levels can also occur. The topical route is intended to reduce systemic exposure and adverse events.

DMSO (dimethyl-sulfoxide) is an organic sulfur compound found naturally in plants and biologic tissues. It has some anti-inflammatory properties and was approved by FDA in 1978 for topical intra-vesical instillation in the treatment of symptomatic interstitial cystitis as a 50% solution (Rimso-50). DMSO has not been found to be safe or effective in other conditions. DMSO can initiate the liberation of histamine and occasionally can produce general hypersensitivity reactions. Changes in the refractive index and lens opacities have been described in some animal species but have not been confirmed in monkey or man. DMSO produces a peculiar (garlic-like) taste and smell on breath. Safety and effectiveness in children have not been established, and caution is recommended to lactating and pregnant women because of potential teratogenic effects as described in some animal species. There are no adequate controlled studies in pregnant women

The risk to benefit balance of Pennsaid as a topical treatment for OA in adults was found to be acceptable by the previous reviewer (Dr. Lapteva), despite modest efficacy findings. Dr. Lapteva concludes that this product can be looked upon as beneficial for the large diversity of patients with OA who may find this preparation as a useful treatment option.

REGULATORY HISTORY- RECENT UPDATE TO NDA 20-947

The initial submission of this NDA occurred on 12/15/1997. The applicant, Dimethaid Research, Inc., submitted a 505(b)(2) application supported by peer review literature with reference to diclofenac sodium and DMSO. The application was withdrawn on October 27, 1998 because the manufacturing facilities were unavailable for inspection. The plant inspection finally took place on ———————— and the facilities were found to be acceptable. b(4)

A non-approvable letter was issued on December 16th, 1998 due to 14 CMC and non-clinical issues and a failure to demonstrate efficacy.

The NDA was resubmitted on August 7, 2001 with supplements on September 20, and October 5th 2001, February 13, March 28, April 3, May 7 and 8, 2002.

After complete review of the information presented, a non-approvable letter was issued on May 22, 2002, citing insufficient information determine if the drug was safe or effective under the proposed conditions of use. Other deficiencies were inadequate information on the pharmacokinetics of DMSO after topical administration, and inadequate information about whether DMSO played a contributing role as an active component of Pennsaid. The applicant was also asked to update the NDA by providing a review of the literature and labels for DMSO, updated information on efficacy and adverse events, and to provide a summary of the worldwide experience with the drug.

A teleconference was held with the applicant on August 29, 2002 to discuss the clinical development strategy. At that meeting the applicant was informed that the development should include a statistical analysis to determine the contribution of DMSO in a factorial study, include laboratory analyses on the 6th week of the trial, institute better pregnancy risk precautions, provide longer and more adequate follow-up for AEs, and to pre-specify abnormal laboratory criteria for study discontinuation.

The Division provided further guidance for the applicant's pivotal clinical study during a meeting of November 4, 2003. Recommendations included using a wider demographic base, adequate laboratory testing including liver function studies, utilizing Patient Overall Health Assessment as a primary end-point, and Patient Global Assessment as a secondary end-point.

The 3rd submission was dated June 28, 2006 and was a Complete Response to the August 7, 2002 Action Letter. After review, an approvable action was taken. This submission included an amended integrated summary of safety (ISS), a clinical safety study and two Phase 3 safety and efficacy studies. These were studies PEN-03-112; a pivotal 12 week randomized study, and study RA-CP-110, a long term safety study, as well as two pharmacokinetic studies, 2656 and 2663. The applicant also submitted additional literature references. There were also, three genetic toxicity studies done in 2003, a

negative mutagenic-carcinogenetic study for DMSO, as well as an ocular and reproductive study concerning DMSO. All these studies were negative.

The following outstanding deficiencies were noted: the need for a demonstration that DMSO does not increase the environmental exposure to toxins or other agents (i.e. sunscreen), genotoxicity, repeat-dose toxicology, and carcinogenic studies of DMSO. There were outstanding bottle and package issues including the need for an assessment of potential extractables from the HDPE bottles, the need for a study of photostability, and the need to tighten the acceptance criteria for the degradation impurities. A safety database update, including an integrated Phase 3 dataset with detailed case reports and narratives, were also recommended from the clinical standpoint.

On December 28, 2006 an approvable (AE) letter was issued. The letter cited the need for several non clinical studies such as a study of the dermal carcinogenicity of Pennsaid, and inclusion of Solaraze-Gel as a reference drug for the NDA. There were no clinical safety concerns.

The Agency held a teleconference with the applicant on June 4, 2007. The applicant was advised to evaluate the dermal carcinogenicity of DMSO in two species, with full histopathology (12 months minipig and 6 month rodent study).

On February 5th, 2009 the NDA was submitted after completing the requested information and data. This new resubmission has an Integrated Summary of Safety (ISS) amended in response to the December 28, 2006 Approvable (AE) Letter.
To address the Agency's questions arising from the 2006 resubmission, additional clinical and non-cinical studies were done to further evaluate the safety of Pennsaid and improve the label information. These include:

- A drying time study of Pennsaid (Study NRI-1000-07120) to define the period of time after the product application during which the patients must avoid exposure to DEET, or sunscreen active components
- A trans-epidermal water loss study- Effect of Pennsaid on stratum corneum barrier function (Study PEN-07-118) to assess potential effect on stratum corneum barrier
- A relative bioavailability study to Solaraze® Gel (Study PEN-07-116)
- A natural occurrence of DMSO in humans study (Study NRI-1000-08500)
- A 6-month rat chronic dermal toxicity study (Study RD-1000-07-05)
- A 12-month minipig chronic dermal toxicity study (Study RD-1000-07-06)
- An environmental toxin minipig study (Study NRI-1000-08101-01)
- In-vitro genotoxicity studies (LPT Studies No. 21116 and 21371)

EFFICACY AND SAFETY REVIEW SUMMARY

A total of 6482 patients have been exposed to Pennsaid in 20 clinical trials evaluating the safety and efficacy of Pennsaid. In Phase 1 trials subjects were exposed for short periods of time and evaluated for skin irritation, plus two recent studies of the effects of Pennsaid on stratum corneum barrier function and drying time with Pennsaid. The length of exposure in Phase 3 trials to Pennsaid was 4-12 weeks. Uncontrolled studies have followed exposure for up to one year and beyond.

An extensive clinical review of the trials, safety, and efficacy of Pennsaid was previously carried out by Dr. Larissa Lapteva during the review cycle of December 2006.
For specific details of these trials please refer to that review. I will summarize the salient and main features only.

Phase 1 Controlled Clinical Studies
Four Phase 1 studies were carried out to assess skin irritation and sensitization. These were studies 100-89, 101-89-2, 103-93-2, and 103-93-3. The safety data for these studies was included in the ISS of 2001.

Two new studies were conducted to assess the effect of Pennsaid on stratum corneum barrier function and drying time for Pennsaid. These studies will be analyzed in the next section.

Phase 3 Controlled Clinical Studies (Safety and Efficacy)
Six Phase 3 clinical trials evaluated the safety and efficacy of Pennsaid for symptoms of osteoarthritis of the knee ———————————— The safety analysis and the results of these studies were analyzed in Dr. Lapteva's review. There have been no new Phase 3 clinical trials conducted since the 2006 review. b(4)

Efficacy Conclusions
The efficacy of Pennsaid has been demonstrated in two adequate and well controlled studies.

Serious events in controlled Phase 3 trials
There is no change in the AE pattern as compared to the previous review from Dr. Lapteva.

Common Adverse Events
The most common adverse reaction during the seven Phase 3 clinical trials were: skin reactions at the application site: (32%) Pennsaid vs (5%) for placebo, contact dermatitis Pennsaid (9%) vs placebo (2%). Headache and dyspepsia were the other most common ones (10% and 8%).

The majority of skin reactions associated with Pennsaid were described as skin dryness occurring in 15.7% of patients in the study PEN-03-112E, while contact dermatitis

occurred in 3.9-5, 8% of the patients. Contact dermatitis was generally reversible upon drug discontinuation, and the incidence diminished with time.

Post marketing Experience

The applicant states that Pennsaid first became available in Canada under the trade name of ———— Topical Solution in 1994 for compassionate use in the treatment of arthritis. In 2003 it was approved for marketing in Canada and UK under the name Pennsaid, and shortly there-after in Italy and Malta, Greece and Portugal. The company states that it expects approval in several other EU countries. Pennsaid is sold in several Caribbean countries where approval is not required to market the drug. b(4)

The applicant submitted a report on the world experience from April 2003 until March 2006. The safety findings of that report were included in Dr. Lapteva's review. The current ISS 2008 is a summary of worldwide experience for the period May 2003-December 2008. This is noted in the applicant's Tables #35 and 36 listed below under column ISS 2008, with another column of comparison for the data of 2006. These reports represent spontaneous reports to the applicant by Medicines and Healthcare Regulatory Agency Products of Canada (MHRA). The majority of these reports originated in the Canadian market where it has been approved since 2003. The AE profile noted was similar to that of the Phase 3 trials.

Table 35 was provided by the applicant and illustrates case reports by body system as explained above. The most frequent reaction reported was skin application site reaction, contact dermatitis, or dry skin.

Table 35: Post-marketing Adverse Reactions by Body System

Body System	Number of Events	
	ISS 2006[1]	ISS 2008[2]
All	117	188
Body as a whole	35	58
Cardiovascular	2	3
Digestive	12	18
Endocrine	0	0
Hemic & lymphatic	0	0
Metabolic & nutritional	1	1
Musculoskeletal	2	3
Nervous	14	26
Respiratory	5	7
Skin & appendages	29	46
Special senses	17	25
Urogenital	0	1

[1]Reporting period: May 2003 – March 31, 2006
[2]Reporting period: May 2003 – December 31, 2008

Table 36 from the applicant's submission (page 60), illustrates post-market adverse reactions to skin and appendages. It quantifies the number of events reported. The first column shows the reported cases from May 2003-March 31, 2006. The second column shows the reported cases from May 2003 to December 31, 2008.

Table 36: Post Marketing Adverse Reactions-Skin

Skin and Appendages		
Application site reaction	0	2
Contact dermatitis, app. site	6	13
Contact dermatitis with vesicles, app. site	2	3
Dry skin, application site	6	8
Eczema	1	1
Pruritus	0	1
Pruritus, app. Site	1	3
Rash	7	4
Rash, app. site	0	3
Skin discoloration	4	5
Urticaria	2	3

The Post-Marketing reports show no new or unexpected events.

New Studies

The current submission contains two new clinical studies: a drying time study (# NRI-1000-07120), and a transepidermal water loss study (#PEN-07-118), to address labeling questions. These studies showed no unexpected or new safety findings.

Study # NRI-1000-07120 was intended to address the issue of the appropriate waiting time required prior to application to same site of other substances (DEET, sun block etc) to the skin, after Pennsaid, in order to avoid the potentially enhanced skin penetration provided by Pennsaid (DMSO).

Study Design

Study # NRI-1000-07120 was a single-dose, open-label, Phase 1 study in 12 normal healthy subjects. Each subject received a dose of 0.15 mL Pennsaid applied to a 100 cm^2 area of the knee skin. The dosed area remained un-occluded during the study. Visual and blotted assessments were made pre-dose and following application at 2, 5, 10, 20, 30, 60, 120, and 240 minutes after application to the treated area. Assessments were conducted on nine separate 3 cm x 3 cm patches within the 100 cm^2 dosed area. Nine post dose assessments were conducted on the nine tested sites in sequence starting at one corner. Only one site was assessed for each post dose assessment time point. The visual assessment of the dose site was scored using a scale of 1-5 (1 = wet shiny; with clear look of solution present, 5 = no visible film).

Testing for adsorption and adherence was done using 3cm x 3cm KimWipes applied to the section and removed by forceps five seconds after placement. Scoring was based on a

scale of 1-3 (1 = distinct adhesion, 3 = no adhesion) and adsorption of water was also assessed using a 1 to 3 scale. Assessment of the weight of the tissue was made before and after tissue placement. Mean weights and scores were analyzed before and after application.

Study Results
The study was completed by all subjects. The results of this study indicated that skin dryness occurred at 10 minutes post-dose in most subjects, confirmed by visual appearance, adhesion, and fluid adsortption. The drying parameters are enclosed in the table below provided by the applicant.

Parameter	Time, minutes [Mean (95%CI)]
Visual appearance of dryness	15.0 (9.6 – 20.4)
No adhesion to the test site	10.0 (NA)
No fluid adsorption to the tissue	10.4 (8.8 – 12.1)
Time to 10% or Less of Peak Weight Recovered	14.2 (8.3 – 20.1)

SAFETY RESULTS: There were no adverse events reported during this study.

Study PEN-07-118, a water loss study was intended to assess the effect of multiple doses of Pennsaid on stratum corneum barrier function to provide information on sources of skin irritation and dehydration (water loss).

Study PEN-07-118 was an open-label, active-controlled, Phase 1 study in a group of 15 healthy non-smoking adult male and female subjects. There was a pre-requirement of no topical skin applications for 1 week prior to the study. Female subjects were required to be pre or post-menopausal. The duration of the study was approximately 12 weeks. Transepidermal water loss (TEWL) was quantified using a vapometer, a closed chamber evaporimeter.

Period 1 (baseline) included measurement of TEWL on Days -7, -5 and -3 prior to first application and then on Day 1.
Period 2 subjects apply study drugs for a period of six weeks. TEWL was measured on each 4 x 4 cm. test site immediately before the application of the morning dose of the study drug on Days 1, 3, 5, 8, 15, 22, 29, 36, and 43. Each subject applied one drop of approximately 30µL of Pennsaid to a 16 cm^2 test site on the right or left volar forearm as randomized, four times a day for six weeks. Each subject also applied a dab of approximately 12 gm of Retina-A to a separate test site on the opposite volar forearm once per day for six weeks

Period 3 (recovery) two weeks following the treatment period was allowed for recovery. TEWL was measured on Days 45, 47, 50, and 58.
Period 4 (Retin-A Challenge) on Days 58-71 Retin-A was applied under occlusion to the same test site as during Period 2. A designated member of the staff applied two dabs of approximately 24 gm of Retin-A to the assigned area once daily for 14 days.

Summary of Results
Nine of the 15 subjects completed all phases of the study. Treatment with Pennsaid did not cause an increase in TEWL compared with the untreated side following six weeks of treatment at a dose consistent with the proposed labeling. No difference was noted between Pennsaid and Retin-A during the treatment period. Neither drug resulted in an increase in TEWL.

The protocol was amended to include an additional challenge period with a double dose of Retin-A under occlusion to induce skin irritation which did result in an increase in TEWL. The applicant believes that the results of the challenge period validates the study results by demonstrating that the subjects were responsive to the enhanced positive control, a known skin irritant.

Safety Results
There were no deaths or serious adverse events. There were 51 adverse events, of those, 35 were of mild severity and classified as probably related to the test article (32 events).

The majority of the events were skin irritation responses including contact dermatitis, dry skin, and pruritus. These were observed at the Retin-A application sites of all subjects (14/15) except for one who reported "dry skin" and occurred at the Pennsaid treated site in only one patient. Fourteen of 15 subjects treated with Pennsaid reported no skin irritation. One subject had dryness and flaking with Pennsaid as mentioned previously. Two subjects experienced changes in laboratory evaluations, glucose, ALT, and AST elevation. All were considered mild and unrelated to the test article. There were no clinical findings related to vital sign alterations.

Findings of study PEN-07-118
In conclusion the applicant reports that chronic dosing with Pennsaid using a dose per cm^2 similar to the proposed label there was no significant alteration or increase of the TEWL, indicating no alteration by Pennsaid of the stratum corneum barrier function.

Study PEN-107-116 was a PK study comparing the absorption of Pennsaid and Solaraze 3%. Thirty subjects with actinic keratosis were enrolled in the study, and received 40 drops of Pennsaid qid to both knees and 0.02 g of Solaraze gel. No serious AEs were reported in this study. Six subjects on Pennsaid (20%) experienced mild AEs while seven subjects (25%) had 14 mild adverse effects with Solaraze. One application site reaction occurred with Pennsaid and five with Solaraze. The most frequent AE reported was rash at the site of application. One subject had a post-study elevation in aminotransferase to 3 times upper limit of normal and aspartate aminotransferase to 2.5

times upper limit of normal but it is unclear to what testing group this individual belonged.

The incidence of skin eruptions and dryness was found to be approximately 20% with repetitive use, that is within the expected range previously observed in the studies.

Summary and Conclusions

Pennsaid is a topical solution containing diclofenac sodium as the active ingredient, and ——————— propylene glycol as a penetration enhancing carrier. It also contains propylene glycol, glycerin, ethanol, and purified water. The intended indication is for the treatment of knee osteoarthritis. b(4)

The clinical program was analyzed in the previous review cycle. Two adequate and well controlled studies of 12 weeks duration have provided evidence of efficacy, with statistically significant improvements noted in pain, physical function, and PGA scores of patients that were treated with Pennsaid. Pennsaid has been compared to placebo and DMSO at two strengths (4.5 and 45.5%) showing similar effects to placebo at both strengths. Approximately 6000 patients were treated with Pennsaid in the development program. From the standpoint of safety the adverse event profile of Pennsaid is similar to approved oral formulations of diclofenac sodium, with additional skin reaction at the site of application. Adverse events also occur in the gastro-intestinal tract though less often than in patients treated with oral diclofenac. The risk of cardiovascular events is similar to oral diclofenac after three months of treatment. Less liver toxicity is observed with Pennsaid than in a comparative group of oral diclofenac. Pennsaid has not been studied in the pediatric population, pregnant or lactating women, and patients with hepatic and renal disease. Patients older than 65 years of age developed more application site reactions than younger aged patients.

The current submission has an updated ISS, that covers the period of May 2003 until December 2008, and contains a listing of new events observed in the last 2 years. This explains the slightly higher number of cases in each category for the 2003-2008 period since it covers a longer period of observation (5 years vs. 3 years). In a few rare instances however, the total number of cases in the most recent ISS are less than in the 2003-2006 period listing (pain: 9 vs 6 cases, rash: 7 vs. 4 cases). The sponsor indicated that the difference was due to re-coding of ADR's. No new deaths were reported.

This submission has two new Phase 1 studies and one PK study. No new or unexpected safety findings were present in these studies. One study demonstrated that dryness of skin occurs between 10-15 minutes after application. Another phase 1 study demonstrated no increase in TEWL or evidence of damage to the stratum corneum of the skin after Pennsaid application.

In conclusion Pennsaid is a modesty effective drug for the treatment of patients with mild to moderate osteoarthritis of the knee, based on the sustained effect noted in the pivotal studies. The safety profile of Pennsaid is considered acceptable and similar to the orally approved diclofenac sodium formulation (Voltaren SR), with additional application site reactions related to Pennsaid. Application site reactions have also been observed with other NSAIDs applied to the skin. The use of Pennsaid in combination with oral NSAIDs is not recommended due to increased adverse events including rectal hemorrhage, hepatic, and renal toxicities.

Recommendation on Regulatory Action

This clinical reviewer agrees with the findings of the previous reviewer (Dr. Lapteva) and recommends approval of Pennsaid for improving signs and symptoms of mild to moderate osteoarthritis of the knee. Collecting and analyzing post market reports of retinal detachment and cataract appearance and progression as well as a pregnancy registry are also recommended.

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/s/

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7/9/2009 03:31:50 PM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	20947
Submission Code	Not applicable
Letter Date	June 28, 2006
Stamp Date	June 28, 2006
PDUFA Goal Date	December 28, 2006
Reviewer Name	Larissa Lapteva, MD, MHS
Team Leader	Jeffrey Siegel, MD
Division Director	Bob A Rappaport, MD
Review Completion Date	December 5, 2006
Established Name	topical solution w/w 1.5% diclofenac sodium
(Proposed) Trade Name	PENNSAID
Therapeutic Class	Non-steroidal anti-inflammatory drug
Applicant	Dimethaid International Inc.
Priority Designation	S
Formulation	Topical solution (1.5% diclofenac sodium, 45.5% dimethyl sulfoxide, —— propylene glycol, —— glycerine, ——ethyl alcohol —————— purified water
Dosing Regimen	40 drops 4 times a day to the affected knee
Indication	osteoarthritis of the knee
Intended Population	primary osteoarthritis of the knee

b(4)

Table of Contents

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This new drug application (NDA) is for approval of a topical solution containing 1.5% diclofenac sodium (proposed trade name: PENNSAID®) for reducing signs and symptoms of osteoarthritis of the knee in adult patients. Four multi-center, randomized, double blind, placebo and vehicle controlled studies in patients with knee osteoarthritis (108-97, RA-CP-109, RA-CP-109-US, PEN-03-112) provide evidence of modest efficacy of PENNSAID®. Seven multi-center, randomized, double blind, placebo- and vehicle- controlled studies (102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US, RA-CP-110, PEN-03-112) and one open label, uncontrolled, long term safety study (PEN-03-112E) provide evidence of the safety of PENNSAID®.

PENNSAID® is a topically applied solution containing 1.5% diclofenac sodium (non-steroidal anti-inflammatory drug-NSAID) as its active ingredient. An oral formulation of diclofenac sodium is approved for treatment of signs and symptoms of osteoarthritis and is marketed in the United States under the following trade names: Voltaren® (Novartis Pharmaceuticals; approved on July 28, 1988), Voltaren XR® (Novartis Pharmaceuticals; approved on November 24, 1993), Cataflam® (Novartis Pharmaceuticals; approved on March 8, 1996) and Arthrotec® (Searle & Co; approved December 24, 1997). Topical formulations of various NSAIDs are widely available in Europe, but there are currently no topical formulations of any NSAID approved for treatment of osteoarthritis in the United States.

PENNSAID® has an adverse event profile similar to that of the oral formulation with diclofenac sodium (Voltaren®). While occurrence of some of the systemic adverse events is diminished with PENNSAID® treatment due to the lower systemic levels of diclofenac sodium owing to the trans-dermal route of administration, application site skin reactions are seen with PENNSAID® treatment, but not with oral diclofenac treatment. The risk benefit ratio of this product appears acceptable for the population of patients with knee osteoarthritis. However, in view of the modest efficacy of PENNSAID® and its safety profile, not all patients will be able to tolerate PENNSAID®. Given the high prevalence of osteoarthritis of the knee and its impact on public health, the diversity of patients' characteristics, and, in most cases, the reversibility of the skin reactions, addition of a topical formulation of a non-steroidal anti-inflammatory drug to the armamentarium of OA treatments will likely benefit a large population of patients and will broaden treatment options for such a prevalent condition as osteoarthritis of the knee.

This clinical reviewer recommends approval of PENNSAID® for treatment of signs and symptoms of knee osteoarthritis.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No special risk management actions are recommended.

1.2.2 Required Phase 4 Commitments

There are no required phase IV commitments.

1.2.3 Other Phase 4 Requests

The Sponsor should conduct a phase IV study investigating ECG changes (including QTc interval changes) in patients receiving PENNSAID®. A study of ECG changes is not required prior to approval because diclofenac is approved for systemic use and because review of the safety database did not reveal a safety signal of arrhythmias to suggest QT prolongation.

This reviewer recommends the Sponsor also agree to:

1. Collecting and analyzing post-marketing spontaneous reports on the incidence rate of retinal detachment and cataract appearance and progression in patients treated with PENNSAID®.
2. Conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to PENNSAID® to identify the pregnancy outcome and postnatal health status of children.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

PENNSAID® is a topical solution containing 1.5% [16mg/ml] diclofenac sodium (active ingredient), 45.5% dimethyl sulfoxide (penetration enhancing carrier), ——— propylene glycol, ——— glycerin, ———ethanol ——— and ——— purified water. This formulation was developed for trans-dermal delivery of the non-steroidal anti-inflammatory medication diclofenac sodium to joints affected by primary osteoarthritis (OA). b(4)

Seven multi-center, randomized, double blind, placebo and vehicle controlled studies (102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US, RA-CP-110, PEN-03-112) were included in the PENNSAID®'s clinical development program. Two adequate and well controlled studies (RA-CP-109-US, and PEN-03-112) of 12 week duration provided the primary evidence of the efficacy of PENNSAID® and were supported by evidence of efficacy from two less well designed studies of shorter duration (108-97, RA-CP-109).

Different placebo formulations were used in different studies. Thus, in study PEN-03-112 the primary comparison was between PENNSAID® and placebo containing 2.3% DMSO; in studies RA-CP-109 and RA-CP-109-US, the primary comparison was between PENNSAID® and placebo containing 45.5% DMSO; and in study 107-96, PENNSAID® was compared to both the placebo formulation containing 4.5% DMSO and the placebo formulation containing 45.5% DMSO. Despite the difference in DMSO concentration, the effects of all the placebo formulations appeared similar between the studies.

Despite over 6000 patients treated with PENNSAID® in its development program, the reliable safety database includes data on 911 patients treated with PENNSAID® among the total of 2512 patients treated in the seven phase III clinical trials and 793 patients exposed to PENNSAID® in study PEN-03-112E. It was previously noted by the Agency and concurred by the Sponsor that the two uncontrolled studies EDR and 105-95 that included more than 4000 patients were not conducted in accordance with GCP. Therefore, the data originating from these two studies were not considered reliable and were excluded from the overall assessment of safety.

The long term safety database includes 144 patients treated with PENNSAID® for at least 12 months.

1.3.2 Efficacy

Analysis of the primary and secondary endpoints in four clinical trials (including two pivotal studies) provides statistically strong and consistent support for modest efficacy of PENNSAID®. Subgroup and sensitivity analyses further support the clinical benefit of PENNSAID®. Studies PEN-03-112 and RA-CP-109-US provide the principle evidence demonstrating the efficacy of PENNSAID® in patients with osteoarthritis of the knee.

Both pivotal studies demonstrated statistically significant improvement in pain and physical function measured with the WOMAC (Western Ontario and McMaster University) Index's pain and physical function dimensions (WOMAC Likert 3.1).

In study PEN-03-112, the mean level of pain in patients treated with PENNSAID® improved by 6 points on a scale of 0-20 after 12 weeks of treatment, which corresponded to a 1.3 point difference in effect between the PENNSAID® and placebo (2.3% DMSO) treatments. Additionally, significantly more patients treated with PENNSAID® achieved at least 10 % improvement in their pain level than patients treated with placebo (86% vs 74%). In the same study, mean scores on a physical function questionnaire improved by 15.8 points on a scale of 0-68 after 12 weeks of treatment with PENNSAID®, which corresponded to a 3.4 point difference in effect between the PENNSAID® and placebo (2.3% DMSO) treatments.

In study RA-CP-109-US, the mean level of pain in patients treated with PENNSAID® improved by 5.9 points on a scale of 0-20 after 12 weeks of treatment, which corresponded to a 1.5 point difference in effect between the PENNSAID® and placebo (45.5% DMSO) treatments. In the

same study, the mean physical function score improved on average by 15.3 points on a scale of 0-68 after 12 weeks of treatment with PENNSAID®, which corresponded to a 5 point difference in effect between the PENNSAID® and placebo (45.5% DMSO) treatments.

Improvement in patient global assessment (PGA) of the study knee was the third co-primary endpoint in study RA-CP-109-US and was a secondary endpoint in study PEN-03-112. In study PEN-03-112, mean PGA improved by 1.4 points on a scale of 0-4 after 12 weeks of treatment with PENNSAID®, which corresponded to a 0.4 point difference in effect between the PENNSAID® and placebo (2.3% DMSO) treatments. In study RA-CP-109-US, mean PGA improved by 1.3 points after 12 weeks of treatment with PENNSAID®, resulting in a 0.3 point difference in effect between PENNSAID® and placebo (45.5% DMSO) treatments.

In study PEN-03-112, significantly more patients in the PENNSAID® group achieved high and moderate improvement according to OMERACT-OARSI criteria[16-17] compared to the placebo group (75% vs 61%). In study RA-CP-109US, significantly more patients in the PENNSAID® group achieved high and moderate improvement according to OMERACT-OARSI criteria[16-17] compared to the placebo group (74% vs 59%).

In study PEN-03-112, the third co-primary endpoint was the Patient Overall Health Assessment (POHA) question. Mean POHA scores improved by 1 point on a scale of 0-4 after 12 weeks of treatment with PENNSAID®, which corresponded to a 0.6 point difference in effect between the PENNSAID® and placebo (2.3% DMSO) treatments.

In the two supportive placebo-controlled studies (RA-CP-109 and 107-96) similar statistically significant improvements in pain, physical function, and PGA scores were observed in patients treated with PENNSAID®.

Overall, the data support the claim that PENNSAID® therapy modestly reduces the signs and symptoms of knee osteoarthritis in patients with mild and moderate knee OA.

1.3.2.1 Other phase III clinical studies in the development program.

Two other studies of short duration and deficient design (study 102-93-1 in patients with knee osteoarthritis and study 108-97 in patients with ———————— failed to demonstrate statistically significant benefit of PENNSAID® treatment over placebo treatment. Descriptive data from a non-inferiority study # RA-CP-110 that compared PENNSAID® and oral diclofenac showed a slightly higher response rate with treatment with oral diclofenac compared to PENNSAID® treatment. b(4)

1.3.3 Safety

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 and form the primary evidence of safety.

The adverse event profile of PENNSAID® was similar to that of the approved oral formulation of diclofenac sodium with the additional adverse event of application site skin reactions. In the controlled phase III trials, application site skin reaction was the most common AE related to PENNSAID® administration compared to placebo. Application site skin reactions consisted of: dry skin- 32% vs 5%, contact dermatitis- 9% vs 2%, contact dermatitis with vesicles 2% vs 0. In the open label study PEN-03-112E, 25% of patients developed dry skin, 13% developed contact dermatitis and 10% developed contact dermatitis with vesicles.

Adverse events related to the gastrointestinal tract, such as dyspepsia, abdominal pain, flatulence, diarrhea, nausea, constipation, and melena occurred in a higher proportion of patients treated with PENNSAID® compared to placebo, but the observed rate of each of these AEs was lower in the PENNSAID® treated patients than in patients treated with oral diclofenac.

The risk of cardiovascular events was similar with PENNSAID® treatment compared to oral diclofenac. The incidence of hypertension with PENNSAID® treatment was similar to that of orally administered NSAIDs.

The frequency of occurrence of edema and peripheral edema as well as increase in creatinine and urea were higher in the PENNSAID® group compared to placebo but lower compared to the oral diclofenac group after 3 months of treatment. After prolonged treatment with PENNSAID®(6-12 months), the rates of these AEs increased.

In the PENNSAID® group, more patients developed elevations in liver function tests compared to placebo. However, less liver toxicity was observed in the PENNSAID® group compared to oral diclofenac.

Patients treated with PENNSAID® had more pronounced decrease in hemoglobin as compared to patients treated with placebo, but less than patients treated with oral diclofenac after 3 months of treatment. More patients developed changes in hemoglobin after 12 months of treatment with PENNSAID®.

Safety assessment of the combination arm (PENNSAID® plus oral diclofenac) showed that the toxicity of oral diclofenac was augmented by addition of PENNSAID®. This was reflected in higher rates of occurrence of GI symptoms, edema, severe skin reactions, elevation in creatinine, urea, liver enzymes, and decrease in hemoglobin and hematocrit in the combination arm compared to the oral diclofenac arm. Risk of rectal hemorrhage was increased with combination treatment.

Overall, the lessened adverse effects on the GI tract, kidneys, liver, and hematological parameters achieved by PENNSAID® are balanced by the increased rate of application site reactions related to the topical administration of diclofenac sodium in PENNSAID®.

1.3.4 Dosing Regimen and Administration

The proposed dose for administration of PENNSAID® (40 drops 4 times /day) was chosen empirically. The proposed dose of 40 drops will equate to 1.2 mL PENNSAID® to an affected knee, 4 times daily. With this formulation the concentration of diclofenac sodium in the solution is 16.05 mg/ml. A daily dose of PENNSAID® of 4.8 mL (4 x 1.2 mL) per knee will result in topical dermal application of ~77 mg of diclofenac sodium to one affected knee daily. The dose will be two-fold higher when applied to both knees. The selected dose and regimen was used in the majority of phase III clinical trials, including the two 12 week studies of efficacy, and appears to provide adequate safety and efficacy of PENNSAID®.

The mechanism of the clinical effect of PENNSAID® is unclear, but is believed to be reduction of pain and inflammation due to direct delivery of diclofenac sodium to the affected joint and the surrounding soft tissue. Results of pharmacokinetic studies have shown that the systemic levels of diclofenac achieved after a single dose topical application of PENNSAID® to two knees (40 drops to each) were 187-200 times lower than after a single oral dose of 50 mg Voltaren ® XR.

The proposed empiric dose appears to provide an adequate safety margin. There are no dose modifications from the proposed dose.

1.3.5 Drug-Drug Interactions

The anticipated drug-drug interactions for PENNSAID® lie in the spectrum of those of the approved oral formulation of diclofenac sodium (Voltaren® XR). No formal studies of the potential for drug interaction with PENNSAID® were conducted by the Sponsor. There were no adverse event reports regarding interactions of other drugs with PENNSAID® in the development program.

1.3.6 Special Populations

Efficacy and safety of PENNSAID® has not been studied in the pediatric population, or pregnant and/or lactating women. PENNSAID® must not be used in these special patient populations. Patients older than 65 years of age developed more application site reactions compared to patients younger than 65 years (see section 7.4.2.3).

2 INTRODUCTION AND BACKGROUND

Osteoarthritis (OA) is a chronic, slowly progressive musculoskeletal disorder that affects weight bearing joints such as the knee and the hip as well as joints of the hand and spine. It is the most common articular disorder with an estimated 21 million adults afflicted by OA[1]. The prevalence of osteoarthritis increases with age, as epidemiological studies have shown that in the Western populations radiographic evidence of OA occurs in the majority of people over the age 65 and in about 80% of those aged over 75. Osteoarthritis is the leading cause of work disability in the United States.

Important risk factors for OA include age, genetic predisposition, and systemic factors such as gender, obesity, reproductive variables, osteoporosis and hypermobility. Local biomechanical factors such as joint shape, trauma, occupation and selected activities dictate the site and severity of joint destruction. Knee is one of the commonly affected joints in OA. Each of the three of its compartments can be afflicted but the medial compartment isolated or in combination with patello-femoral disease are the commonest forms. Patients presenting with knee OA generally fall into two categories: younger people, often males, with oligoarthritis secondary to previous injury and middle aged older people, predominantly females, who present with OA involving both knees along with symmetrical joint involvement in other sites. The condition is characterized by joint pain, crepitus, stiffness after immobility, and limitation of motion. The clinical signs and symptoms are associated with defects in the articular cartilage and underlying bone. The slowly progressing joint damage leads to impairment in physical function resulting in disability and reduced quality of life.

Non-sterodal anti-inflammatory drugs (NSAIDs) are often used for treatment of osteoarthritis including treatment of knee OA. They block cyclo-oxygenase, thereby inhibiting biosynthesis of prostaglandins, known inducers of pain and tissue inflammation. Administered orally, NSAIDs bring relief of pain and a decrease in inflammation but can also cause well known undesirable side effects related to systemic administration. The rationale for development of a topical formulation containing an NSAID was to provide local analgesic and anti-inflammatory effects while minimizing systemic effects.

2.1 Product Information

PENNSAID® is a topical solution containing 1.5% [16mg/ml] diclofenac sodium (active ingredient), 45.5% dimethyl sulfoxide (penetration enhancing carrier of diclofenac sodium), ——— propylene glycol, ——— glycerin, ——— ethanol, ——— and ——— purified water. b(4)
This formulation was developed for trans-dermal delivery of the non-steroidal anti-inflammatory medication diclofenac sodium to a joint affected by primary osteoarthritis (OA).
The current new drug application is proposing the indication for PENNSAID® of treatment of signs and symptoms of primary osteoarthritis of the knee(s). The proposed dose for use in patients with knee OA is 40 drops (1.2 mL PENNSAID®) to an affected knee, 4 times daily, which calculates to the daily dose of PENNSAID® of 4.8 mL (4 x 1.2 mL) per knee, resulting in

topical dermal application of ~77 mg of diclofenac sodium to one affected knee daily. The dose will be two-fold higher when applied to both knees.

2.2 Currently Available Treatment for Indications

Currently, several groups of medications are available for treatment of primary osteoarthritis of the knee(s). These include topical, oral, and intra-articular treatments. Of the topical treatments, capsaicin cream (Zostrix®) and topical salicylates (Aspercreme®) are available. Of medications administered orally, non-steroidal anti-inflammatory drugs (including oral diclofenac sodium, Voltaren® approved on July 28, 1988), acetaminophen-based products, and analgesics (including opioid analgesics) are available for treatment of primary OA. Intra-articularly administered corticosteroids (Kenalog®) and viscosupplementation (Synvisc® , Hyalgan®) are available as intra-articular treatments for knee OA. No topical non-steroidal anti-inflammatory medications are currently available for treatment of primary OA in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

In the United States, PENNSAID® is currently an investigational new drug. Its active ingredient, diclofenac sodium, is presently marketed in the United States for treatment of signs and symptoms of OA as an oral formulation under the trade names Voltaren® (Novartis Pharmaceuticals; approved on July 28, 1988), Voltaren XR® (Novartis Pharmaceuticals; approved on November 24, 1993), Cataflam® (Novartis Pharmaceuticals; approved on March 8, 1996) and Arthrotec® (Searle & Co; approved December 24, 1997). A topical product containing 3% diclofenac sodium (Solaraze®, Bradley Pharmaceuticals) was approved for treatment of actinic keratosis on October 16, 2000 and is currently marketed in the US for this indication.

2.4 Important Issues With Pharmacologically Related Products

With oral diclofenac and other NSAIDs, major safety concerns include increased risk of thromboembolic cardio-vascular events and increase in blood pressure, liver toxicity related to the hepatic metabolism accounting for the drug elimination, renal toxicity due to effects on renal prostaglandins, irritation effect on the GI tract mucosa and an increased risk of subsequent GI ulceration, bleeding and perforation. Additionally, fluid retention and edema have been observed in some patients receiving oral diclofenac. Potential hematological effects include anemia (possibly related to GI loss, fluid retention or unknown effects on erythropoiesis) and interference with platelet function and vascular responses to bleeding related to inhibition of prostaglandin biosynthesis. Exacerbation of conditions with underlying broncho-constriction has also been observed in patients treated with oral diclofenac. Severe allergic reactions are of the same degree of concern as with other NSAIDs. These safety concerns are also potential concerns with topical diclofenac sodium, although the degree of risk should be lessened based on the reduced systemic levels with topical application.

As with the 3% topical diclofenac gel (Solaraze®) approved for treatment of actinic keratosis on October 16, 2000, major safety concerns for skin toxicity associated with PENNSAID ® include contact dermatitis, pruritis, rash, skin desquamation and exfoliation.

One of the excipients of the proposed formulation is DMSO (dimethyl sulfoxide-45.5%), which is considered an inactive ingredient used to enhance dermal penetration of diclofenac sodium. This inactive ingredient constitutes an active component of RIMSO-50® topical solution used for intra-vesicular irrigations approved by FDA in 1978 (NDA-17-788) for treatment of interstitial cystitis. A warning on the RIMSO-50 label (PDR 1980) specifically states that topical (as opposed to intra-vesicular) application of DMSO can cause liberation of histamine causing occasional hypersensitivity/anaphylactoid reactions. It is recommended in the label that liver and renal function and complete blood count be checked every 6 months while on chronic treatment with RIMSO-50. Other possible effects associated with application of high doses (90%) DMSO reported in the literature[3,2,5, 18, 19, 20] include nausea, headaches, dizziness, sedation, vasodilation, burning and aching eyes, transient disturbances in color perception, anorexia, garlic-oyster-like odor in body and breath, transient hemolysis and hemoglobinuria and possible dose-dependent hematuria. One case of severe sensory-motor peripheral neuropathy has been reported with use of topical application of 90% DMSO concomitantly with an NSAID sulindac[14]. Some animal studies demonstrated increased risk for development of lens opacities and changes in ocular refractive index in dogs, and rats[2], but studies in primate monkeys[4] and in humans[6,7,8,9] did not confirm this risk.

2.5 Presubmission Regulatory Activity

PENNSAID® (NDA 20-947) was initially submitted as a new drug application by its Sponsor Dimethaid International Inc. on December 15, 1997, but withdrawn by the Sponsor on October 27, 1998. Nonetheless, the non-approvable letter issued for that submission on December 16, 1998 included 14 chemistry issues and a reference to the fact that one of the submitted pivotal studies (#102-93-1) failed to demonstrate statistical significance and did not provide substantial evidence of efficacy.

The second submission was re-submitted as a stand alone submission on August 7, 2001. The second non-approvable letter was issued on August 7, 2002 and included several deficiencies regarding evaluation of PENNSAID®'s efficacy and safety. After the second non-approvable letter, the Sponsor requested guidance from the Division in regard to design of future studies and compliance with current FDA regulations.

The design of future studies was discussed during subsequent meetings (meeting minutes from: September 10, 2002; November 4, 2003) and teleconferences (minutes from: August 29, 2002; November 19, 2002; January 6, 2003 and January 16, 2003). Additional general advice letters were sent to the Sponsor on October 21, 2002, November 5, 2002, and December 6, 2002.

To fully respond to the indicated deficiencies the Sponsor conducted two additional clinical studies (five arm trial #PEN-03-112 and long term 12 month safety study PEN-03-112E) as well as two additional PK studies (#2663 and #2656). Table 1 below summarizes the clinical

deficiencies identified in the second non-approvable letter dated August 7, 2002 and the actions taken by the Sponsor to fully respond to these deficiencies:

Table 1. Clinical deficiencies indicated in the NA letter from 08/07/2002, and the actions undertaken by the Sponsor to address these deficiencies.

Deficiency	Sponsor's response
1. Demonstration of efficacy at the site of application. Treatment of both the study knee and the contra-lateral knee was allowed in the pivotal studies (RA-CP-109 and RA-CP-109US), while randomization process randomized subjects and not knees	In the new pivotal study (#PEN-03-112) patients were allowed to treat the study knee only; stratification by knee involvement (1 or 2) was done prior to randomization Additionally, the results of study RA-CP-109US were reanalyzed using the data from the study knee only
2. ITT (intent-to-treat) population was inappropriately defined	ITT population was appropriately defined, and the primary analysis of study PEN-03-112 was based on the correct ITT population. Results of studies (RA-CP-109, and RA-CP-109US and 107-96) were reanalyzed on their respective, correctly defined, ITT populations.
3. The main results of the pivotal studies (RA-CP-109 and RA-CP-109US) varied depending on the methods of imputation of missing data	Appropriately conservative, BOCF, method of imputation was used in studies PEN-03-112, RA-CP-109US and RA-CP-109 to support the results of primary analyses
4. DMSO that is viewed by the Sponsor as an inactive ingredient may contribute to the efficacy of PENNSAID®. No adequate demonstration of the adverse event profile of 45.5% DMSO vs PENNSAID® was submitted	The newly designed study PEN-03-112 included an arm containing topical formulation of 45.5% DMSO and no diclofenac sodium, thus allowing evaluation of safety and efficacy of 45.5% DMSO in the placebo- and PENNSAID®- controlled conditions
5. No scheduled measurements of efficacy were done between the baseline and the final study assessments	Efficacy assessments at the intermediate time points were incorporated in the study PEN-03-112
6. Address safety of co-administered therapies, particularly oral NSAIDs	The newly designed study PEN-03-112 included an arm containing a combination of PENNSAID® and oral diclofeanc, thus allowing evaluation of safety of PENNSAID® when co-administered with an oral NSAID
7. Inadequate AE reporting in the long term studies EDR and #105-95. Lack of credible long term safety data from a sample size recommended by ICH guidelines (≥300 patients for 6 months, ≥ 100 patients for 12 months)	Study PEN-03-112E was designed and included sufficient amount of patients as well as safety assessments and patient monitoring for up to 12 months
8. No laboratory data were collected in pivotal	Laboratory data were collected in the newly

studies RA-CP-109 and RA-CP-109US	designed studies PEN-03-112 and PEN-03-112E

Additionally, subsequent to the second NA letter discussions (dates indicated above), the following issues were discussed and addressed by the Sponsor in the study PEN-03-112:

1. Patients were assured to be more symptomatic at baseline (WOMAC pain score of at least 8).
2. Clinically important difference was considered as absolute change of 10% from baseline to final study visits
3. The use of acetaminophen as a rescue medication was specified
4. At the Division's advice, the patient global question (Patient Global Assessment-PGA) was substituted with the Patient Overall Health Assessment-POHA) and the POHA question was used as one of the three co-primary outcomes
5. A variable of patient weight was included in the demographic characteristics
6. Bilirubin was included in the laboratory parameters
7. An additional secondary analysis for comparison of the effect of 45.5%DMSO and 2.3% DMSO (placebo) was added
8. An additional secondary analysis for the use of rescue acetaminophen was added
9. Ophthalmologic evaluations were added to be performed at baseline and final study visits in studies PEN-03-112 and PEN-03-112E to address a potential safety concern about a remote possibility of DMSO causing lens opacities/cataracts seen in animal studies
10. In the general advice letter from October 21, 2006, the Division recommended designing a six arm trial with study arms designed as shown below in Table 2. Consequently, the study PEN-03-112 was designed with inclusion of all the arms recommended but the arm with the combination of DMSO and oral diclofenac. Although the design chosen by the Sponsor did not allow performing factorial analysis, the inclusion of the arm with vehicle control allowed efficacy assessment of the topical 45.5% DMSO.

Table 2. Design of study PEN-03-112 recommended to the Sponsor by the Division.

	Topical	Oral
Group 1	Pennsaid	Diclofenac
Group 2	Pennsaid	Placebo
Group 3	DMSO (45%)	Diclofenac
Group 4	DMSO (45%)	Placebo
Group 5	Placebo (4.5% DMSO)	Diclofenac
Group 6	Placebo (4.5% DMSO)	Placebo

The current (third) submission was submitted on June 28, 2006. Additional clinical information requests (IR) were sent to the Sponsor on August 1, 2006 and September 22, 2006 (biostatistics), August 23 and 24, 2006, October 6 and 20, 2006, November 6, 8 and 9, 2006 (clinical). A teleconference with the Sponsor about the clinical issues was held on August 31, 2006. The Sponsor satisfactorily responded to all the above listed IRs.

2.6 Other Relevant Background Information

PENNSAID® was approved for marketing for treatment of osteoarthritis in the United Kingdom on November 21, 2000, and became available commercially on March 2001. According to the Sponsor, for the period of March 2001 to April 2003, there were no reports of AEs made directly to the Regulatory Agency or to the Sponsor. PENNSAID® was approved in Canada on March 28, 2003. Refer to Section 7.1.17 for AE reports in the post marketing experience worldwide for the period April 2003 to March 2006.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

As indicated in Dr. Sue-Ching's chemistry review, there were no outstanding CMC issues with this submission. Also, no outstanding CMC issues were noted from the last review cycle. The following information was updated in this review cycle: stability data, drug product specification, labeling, drug substance DMF, manufacturing batch records, and container closure system. The updated data and the Sponsor's response to the CMC comments have been found to be adequate. A re-evaluation of all the facilities for the manufacturing, testing, and packaging of the drug substance and drug product was submitted to the Office of Compliance. An overall "acceptable" recommendation was issued for this NDA by the Office of Compliance on August 29, 2006.

Microbiology review from previous submission done by Dr. Bryan Riley (Feb 13, 2002) revealed no pending issues.

3.2 Animal Pharmacology/Toxicology

Animal pharmacology toxicology studies were not conducted by the Sponsor under 505(b)2 in reference to Voltaren®'s respective animal studies. The product information of the dermal carcinogenicity and photocarcinogenicity was insufficient in this submission (see further Pharmacology/Toxicology review by Dr. Leshin).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

EDR document#	Date of submission
2956766	06/28/2006
2992143	09/18/2006
2997226	09/29/2006
3001586	10/11/2006

3002418	10/12/2006
3002902	10/13/2006
3006399	10/23/2006
3007924	10/25/2006
3009481	10/27/2006
3015028	11/08/2006
3015657	11/10/2006
3015628	11/10/2006

Additionally, the following information was reviewed:

1. Consultation with the Division of Ophthalmologic Products was requested by the Division to assist in review of cases of retinal and vitreous disorders.
2. Previous reviews of NDA 20-947 by Drs. Witter, Oussova, Riley, Bashaw, Sue-Ching, Amouzadeh, Hon-Sum Ko, and Dr. Averbuch.
3. Archived original study reports of studies 102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US (originally submitted as paper submissions).

4.2 Tables of Clinical Studies

The product under review for NDA is PENNSAID® topical solution containing 1.5 % diclofenac sodium. During the different stages of drug development different control treatments were used in studies designed to assess the efficacy of PENNSAID®. The Table 3 below shows the constituents of PENNSAID® and different comparator/placebo formulations used in different studies. It is worth to note that in the earlier studies (#100-89, 101-89-2, 103-93-2, 104-93-3, 102-93-1 and 107-96) 4.55% DMSO was used as a placebo solution, whereas in studies conducted later (#PEN-03-112, RA-CP-109, and RA-CP-109 US) the placebo solution contained 2.3% DMSO as indicated in Table 4. At no time during the drug development, placebo solution containing no DMSO was used in any of the studies. The reason for this was difficulty with masking of the DMSO-containing product that in some cases is capable of producing characteristic oyster/garlic-like body odor.

Table 3. Constituents of topical formulations used in PENNSAID® development program

Composition: (%, w/w)	PENNSAID®	Vehicle-control Solution	Placebo Solution
Diclofenac sodium	1.5	0	0
DMSO	45.5	45.5	2.3
Propylene glycol			
Glycerin			
Ethanol			
Purified water			

b(4)

The overall NDA submission for PENNSAID® consists of seven controlled trials (studies #102-93-1 and #107-96 were submitted in the first submission in 1998, studies #108-97, RA-CP-109

and RA-CP-109US were submitted in the second submission in 2001, and studies #PEN-03-112 and #PEN-03-110 were submitted during this current, third submission). Table 2 represents each study's duration, design, and time of submission.

The efficacy review was based on the review of efficacy data from the seven phase III clinical trials shown in Table 4. The two pivotal, 12 week duration, placebo and vehicle controlled studies (# PEN-03-112 and re-analyzed study #RA-CP-109US) were the primary source of efficacy conclusions in this review.

The safety review was based on the safety data from seven phase III clinical trials (102-93-1, 107-96, 108-97, RA-CP-109-US, Ra-Cp-109, RA-CP-110, PEN-03-112) shown in Table 4, as well as the data from the long term study PEN-03-112E.

The four phase I clinical studies evaluating skin irritation and sensitization (100-89, 101-89-2, 103-93-2 and 104-93-3) were reviewed in detail in the Dermatology Consultation report by Dr. Hon-Sum Ko, during the previous review cycle (May 16, 2002), and will be summarized and briefly mentioned in section 7.1.12.

Clinical pharmacology (bioavailability) studies (102-93-1, 106-95, substudy in study RA-CP-109-US, 2663, 2656) were reviewed in the respective reviews of Dr. Bashaw and Dr. Lee and the updates will be summarized in section 5.

Table 4. Clinical Development program for PENNSAID®, data from Sponsor's Table 1, p 8, ISS

Protocol No.	Type of Study	Phase	No. of Patients	Treatments
102-93-1	A double-blinded, three-arm, multi-dose pharmacokinetic study. (sub-study of the controlled trial)	Phase III	(12)[1]	PENNSAID®[2]
106-95	An uncontrolled, single-dose pharmacokinetic study	Phase I	6	PENNSAID®
RA-CP-109-US	A double-blinded, vehicle controlled, two-way parallel, multi-dose pharmacokinetic study. (sub-study of the controlled trial)	Phase III	(23)[3]	PENNSAID®
2663	An uncontrolled, single-dose pharmacokinetic study.	Phase I	18	PENNSAID®
2656	An uncontrolled, multi-dose pharmacokinetic study.	Phase I	20	PENNSAID®
100-89	A double-blinded, 3-arm, single center, irritation and sensitization study.	Phase I	25	PENNSAID® Vehicle-control[4] Placebos High-dose diclofenac control: 10% diclofenac sodium, 45.5% w/w DMSO, ——— glycerin, ——— ethanol; and ——— propylene glycol in water
101-89-2	A double-blinded, 3-arm, single center, sensitization study.	Phase I	223	PENNSAID® Vehicle-control Placebo[5]
103-93-2	A double-blinded, 24-hour, occluded, single center 3-arm, photoirritation study.	Phase I	25	PENNSAID® Vehicle-control Placebo[5]

b(4)

104-93-3	A double-blinded, 3-arm, one center, photoirritation/ photosensitization study.	Phase I	27	PENNSAID® Vehicle-control Placebo[5]
102-93-1	A double-blinded, 3-arm, multi-centered, safety and efficacy trial in the osteoarthritic knee.	Phase III	122	PENNSAID® Vehicle-control Placebo[5]
107-96	A double-blinded, placebo-controlled, 3-arm parallel clinical efficacy and safety trial in the osteoarthritic knee. (4 weeks).	Phase III	248	PENNSAID® Vehicle-control Placebo[5]
108-97	A double-blinded, placebo-controlled, 4-arm, parallel clinical efficacy and safety trial in the osteoarthritic ———	Phase III	203	PENNSAID® Vehicle-control 'Non-DMSO' diclofenac control (1.5% w/w diclofenac sodium, 2.3% w/w DMSO, ———ethanol in water) Placebo[6]
RA-CP-109	A double-blinded, vehicle-controlled, 2-arm, parallel clinical efficacy and safety trial in the osteoarthritic knee (6wks).	Phase III	216	PENNSAID® Vehicle-control
RA-CP-109-US	A double-blinded, vehicle-controlled, 2-arm, parallel clinical efficacy and safety trial in the osteoarthritic knee (12wks).	Phase III	326	PENNSAID® Vehicle-control
PEN-03-112	A double-blinded, vehicle- and drug-controlled (double-dummy), 5-arm, parallel clinical efficacy (equivalency) and safety trial (12 wks).	Phase III	775	PENNSAID® plus Oral Diclofenac (100 mg OD.) PENNSAID® plus Oral Placebo Vehicle-control plus Oral Placebo Topical Placebo[7] plus Oral Placebo Topical Placebo[7] plus Oral Diclofenac
RA-CP-110	A double-blinded, drug-controlled, (double-dummy), 2-arm, parallel clinical efficacy (equivalence) and safety trial in the osteoarthritic knee (12wks).	Phase III	622	PENNSAID® (50 drops t.i.d.) plus Oral Placebo Oral Diclofenac (50 mg t.i.d.) plus topical Placebo[6]
Emergency Drug Release[8] (EDR) (replaced by 105-95 in March 1995)	An uncontrolled, open-ended treatment study of PENNSAID™ in symptomatic arthritis.	EDR	244	PENNSAID®
105-958	An uncontrolled, open-ended study of the safety of PENNSAID® in the treatment of	Phase III	4213[9]	PENNSAID®

b(4)

	arthritis.			
PEN-03-112E	A long-term, multi-center, single-arm, open-label extension safety study	Phase III	793	PENNSAID®

[1]These patients are also counted in the controlled study 102-93-1.
[2]PENNSAID®: 1.5% w/w diclofenac sodium, 45.5% w/w DMSO, ——— glycerin, ——— ethanol, ——— propylene glycol and water
[3]These patients are also counted in the controlled trial RA-CP-109-US.
[4]Vehicle-control: 0% diclofenac sodium, 45.5% w/w DMSO, ——— glycerin, ——— ethanol, ——— propylene glycol in water
[5]Placebo in studies 100-89, 101-89-2, 103-93-2, 104-93-3, 102-93-1 and 107-96 contained 4.55% w/w DMSO, ——— w/w glycerin, ——— ethanol; ——— propylene glycol in water
[6]Placebo in studies 108-97 and RA-CP-110 contained 2.3% w/w DMSO and ——— in water. [7]Placebo in study PEN-03-112 contained 2.3% w/w DMSO, ——— propylene glycol, ——— glycerin, ——— ethanol in water.
[8]This study was not conducted or monitored according to GCP.
[9]Thirty-seven of these patients also participated in the EDR program.

b(4)

4.3 Review Strategy

This clinical development program included seven phase III clinical studies, some of which were not designed as adequate and well controlled studies. Therefore, the primary focus of the efficacy review is the two adequate and well controlled pivotal trials (PEN-03-112 and RA-CP-109-US), with supporting efficacy provided by the studies RA-CP-109 and 107-96. Other phase III studies conducted in this program will be briefly described in section 6.1.4. Phase I studies investigating skin irritation and sensitization are reviewed in Dr. Hon-Sum Ko's review, and the respective pharmacology (bioavailability) studies are reviewed in Drs. Barshaw's and Lee's reviews.

The review of safety is based on the data pooled from the seven phase III controlled clinical trials (102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US, RA-CP-110, and PEN-03-112) and the open label, 12 month, long term safety study PEN-03-112E. These eight trials provide an adequate amount of drug exposure for evaluation of safety of PENNSAID® in subjects with knee OA. Special attention was focused on the occurrence of skin AEs in association with PENNSAID® and the safety profile of the combination of topical and oral diclofenac (Group 1 in study PEN-03-112: PENNSAID® plus oral diclofenac).

4.4 Data Quality and Integrity

In general, the data quality and integrity were adequate. As commented by the previous reviewers, the data quality and integrity were not satisfactory in the previous two submissions. The Sponsor considered the previous comments, and the quality and integrity of the newly designed and submitted studies (PEN-003-112 and PEN-03-112E) were good. The integrity of analyses shown in the Integrated Summary of Safety and Integrated Summary of Efficacy was

adequate and corresponded to the attached source tables. Random datasets were audited with their corresponding tables and the integrity of data was found satisfactory.

Despite over 6000 patients treated with PENNSAID® in the PENNSAID®'s development program, the reliable safety database includes data on 911 patients treated with PENNSAID® in the seven phase III clinical trials and 793 patients exposed to PENNSAID® in study PEN-03-112E. It was previously noted by the Agency and concurred by the Sponsor that the two uncontrolled studies EDR and 105-95 that included more than 4000 patients were not conducted in accordance with GCP. Therefore, the data originating from these two studies were not considered reliable and were excluded from the overall assessment of safety.

DSI consultation was requested for inspection of two centers in Canada and two centers in the US, participating in study PEN-03-112. These four sites were selected based on the considerable number of patients enrolled, higher than the study average response rates and significant numbers of protocol violations. At the time of this review the site inspection has not been completed yet.

4.5 Compliance with Good Clinical Practices

All studies were conducted in accordance with the ethical principles in the Declaration of Helsinki. All studies but studies EDR and #105-95 were conducted and monitored in accordance with Good Clinical Practice. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letter forms for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation.

EDR is Emergency Drug Release Program conducted in Canada from March 1994 to March 1995. In 1995 it was replaced by open-label study #105-95 conducted from 1995 to 1999. The Sponsor concurred with the Division's previous note of adverse event underreporting in these two studies and agreed that they were not conducted or monitored according to the GCP. Consequently, in this review, the long term safety of PENNSAID® was assessed from study PEN-03-112E that was designed in response to the NA letter (August 7, 2002) and conducted and monitored in accordance to GCP.

4.6 Financial Disclosures

The Sponsor has adequately disclosed financial arrangements with clinical investigators as specified in the FDA guidance for industry (Financial Disclosure by Clinical Investigations, CDER, March 20, 2001). As indicated in the Financial Interests and Arrangements of Clinical Investigators FDA form 3454, no clinical investigators disclosed any potential conflict of interest.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The Clinical Pharmacology review from the previous submission by Dr. Bashaw (Aug 1, 2001) indicated that the poor choice of plasma sampling times (baseline and study exits) precluded making definitive statements regarding the potential bioavailability of either diclofenac or DMSO. The following was recommended:

"Based on both the amount of diclofenac contained in this solution and the proposed conditions of use, no additional systemic pharmacokinetic information is needed relative to the diclofenac component of this product. However, you have not provided an adequate evaluation of the pharmacokinetics of DMSO following topical administration. As part of the clinical program for this product, you should undertake a study whereby both single dose and multiple dose pharmacokinetic sampling is undertaken for DMSO and its major metabolites with both an adequate number of samples and subjects. This study must be conducted prior to approval."

In the current submission, as requested by the Division, the Sponsor conducted two studies (a single dose PK study, # 2663 and a multiple dose PK study, # 2656) to assess the bioavailability of diclofenac and DMSO. The overall summary of the two studies is provided below. Refer to Dr. David Lee's Clinical Pharmacology review for detailed review of the studies.

Based on the single-dose Pennsaid® Study 2663, which provides maximally 8.05 ng/mL of diclofenac sodium (40 drops of Pennsaid® to two knees), when compared to a single oral dose of Voltaren® (50 mg tablet; C_{max} was 1500–1600 ng/mL), the maximum blood levels of diclofenac sodium with Pennsaid® were more than 187–200 times lower than with oral administration of diclofenac sodium.

Comparison of the time to reach maximum concentrations after administration of the drug products revealed that it took significantly longer for diclofenac sodium to reach C_{max} after topical application (11 hrs) than oral administration (1–4 hrs). Moreover, comparing the area under the serum concentration time curve for diclofenac sodium between topically applied Pennsaid® and orally administered Voltaren®, the AUC_{0-inf} for Pennsaid® (containing —— diclofenac sodium) was 196.9 ng.hr/mL which was substantially lower than the reported AUC_{0-inf} for enteric-coated Voltaren® (50 mg). b(4)

In study 2663, calculation of the pharmacokinetic parameters of DMSO's metabolite, $DMSO_2$, was not possible since the majority of the concentrations were below the lower level of quantitation (LLOQ).

In study 2656, the daily DMSO dose in Pennsaid® applied was 5.2 g (0.65 mg per knee, four timesa day). On Days 6, 7 and 8, trough plasma concentrations of DMSO were 1.3, 1.0 and 1.1 µg/mL, respectively. DMSO reached plasma concentration levels at or near steady state on Day 6. Following the last dose of Pennsaid® on Day 8, mean DMSO C_{max} was 1.2 µg/mL and mean

T_{max} value was 3.8 hrs. The mean DMSO AUC_{0-inf} was 36.0 µg.hr/mL. The mean apparent terminal half-life ($t_{½}$) was 43 hrs. For $DMSO_2$, plasma trough concentrations on Days 6, 7 and 8 were 15.7 µg/mL, 16.7 µg/mL and 16.5 µg/mL, respectively. These values were not statistically different between each other, when tested by ANOVA model, indicating that $DMSO_2$ reached plasma concentration levels at or near steady state on Day 6. Following the last dose of Pennsaid® on Day 8, $DMSO_2$ C_{max} value was ———— and mean T_{max} value was 9.4 hrs. The mean $DMSO_2$ AUC_{0-t} was 1525.3 µg.hr/mL and the mean AUC_{0-inf} was 2339.2 µg.hr/mL. The mean apparent terminal halflife ($t_{½}$) was 61 hrs. During this study, 11 subjects experienced a total of 34 adverse events. b(4)

Overall, the information contained in this Complete Response for diclofenac, DMSO and $DMSO_2$, were found acceptable. There were no other issues for this Sponsor's Complete Response.

5.2 Pharmacodynamics

In study 2656, 10 patients were randomly selected for platelet aggregation analysis. Based on the results presented for this analysis, the average change from the addition of the aggregation agents ADP, collagen, epinephrine and arachidonic acid were 101.3%, 99.8%, 109.8% and 99.0%, respectively. These results indicated that there was no significant difference between baseline platelet aggregation results and the final platelet aggregation results obtained for the randomly selected subjects who were administered Pennsaid® Topical solution.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor proposes the indication of PENNSAID® for treatment of signs and symptoms of primary osteoarthritis of the knee(s).

6.1.1 Methods

This review of efficacy will focus on the efficacy results of two controlled pivotal studies RA-CP-109-US (efficacy results reanalyzed by the Sponsor on adequate ITT population and resubmitted with the current submission) and PEN-03-112 (study designed with guidance received from the Agency). A brief overview of other studies' efficacy results will be provided.

6.1.2 General Discussion of Endpoints

Osteoarthritis (OA) is a chronic slowly progressing condition afflicting weight bearing joints such as knee and hip as well as joints of the hand and spine. Knee joint is one of the most commonly affected joints in OA with frequent involvement of medial and patellar-femoral compartments. Primary OA is typically characterized by symmetrical joint involvement and

occurs in middle age individuals, predominantly females. Known risk factors for primary OA include age, genetic predisposition, gender, and obesity.

Characteristic symptoms of OA include joint pain, crepitus, stiffness, and limitation of motion and are associated with radiographic changes such as joint space narrowing, subchondral sclerosis and cysts and marginal osteophyte formation. Despite the generally progressing disease course, the symptoms may flare and remit until the late stage of OA when the articular cartilage destruction is advanced and the level of pain is constant. Progressing joint damage leads to variable degree of impairment in physical function, and the resulting disability may severely compromise individual's quality of life.

Consequently, endpoints for clinical trials in OA should be chosen that assess the pain and physical impairment as well as patient's overall assessment of their health.
The most commonly used and best validated OA trial outcome measure is Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). It is a 24 items questionnaire assessing pain (5 items), physical function (17 items) and stiffness (2 items) in patients with knee and hip OA. The current FDA draft guidance for OA clinical trials suggests use of the WOMAC index for pain and physical function (measured separately) as well as the patient's global assessment to be used as three co-primary endpoints. Two trials of 12 week duration are considered necessary to evaluate the efficacy of a new therapy.

In both studies, RA-CP-109US and PEN-03-112 the Sponsor used WOMAC Likert 3.1 OA index for assessment of pain and physical function dimensions as the two first co-primary endpoints. Stiffness was assessed in both studies as a secondary endpoint.
The third co-primary endpoint was Patient Global Assessment (PGA) in study RA-CP-109US; and Patient Overall Health Assessment (POHA) question in study PEN-03-112. The POHA question was designed with the guidance from the Agency and aimed at assessing the response of the osteoarthritic knee to therapy as well as any adverse events that may have occurred. The question was: "Considering all the ways your osteoarthritic (study) knee and its treatment affect you, including both positive and negative effects, how would you rate your overall state of health in the past 48 hours?"

In the PEN-03-112 study protocol the Sponsor indicated that 10% improvement on each scale would be considered as a pre-specified clinically meaningful difference in the scoring of the primary outcomes (i.e. 10mm on 100mm VAS or 2 on a 20 point Likert scale).

While measuring mean changes in the dimensions of interest, the WOMAC index may not adequately reflect individual patients' responses to treatment. Recently proposed, large database derived OMERACT - OARSI criteria for response in OA clinical trials are heavily based on the WOMAC index and seem to capture the individual responders to treatment. The following criteria have been recently proposed for use in OA clinical trials:

I. HIGH IMPROVEMENT. Patient is classified as a responder if s(he) demonstrates high improvement in pain or in function $\geq$ 50% and absolute change $\geq$ (20% of the scale)

II. MODERATE IMPROVEMENT. Patient is classified as a responder if s(he) demonstrates high improvement in at least two of the three following:

-pain $\geq$ 20 % and absolute change $\geq$ 10% of the scale
-physical function $\geq$ 20% and absolute change $\geq$ 10% of the scale
-patient global assessment $\geq$ 20% and absolute change $\geq$ 10% of the scale

At the request of the Agency, the Sponsor conducted a post hoc analysis where patients were classified as responders according to level I (high improvement) or level II (moderate improvement) OMERACT-OARSI criteria, as well as analysis of responders according to the pre-specified 10% improvement in each dimension scale measuring study outcomes.

Both WOMAC index measuring pain, physical function and stiffness and OMERACT- OARSI criteria are acceptable study outcomes measuring clinically meaningful improvement in OA.

Patient Global Assessment is a part of ACR 20 criteria for trials in RA and a part of OARSI criteria for response. It has been widely used in previous trials and is well accepted in the community as an outcome measure of patient's assessment of the status of their disease. Patient's Overall Health Assessment Question, on the other hand, takes into consideration all positive and negative effects of the treatment, while incorporating patient's perception of not only effects of the treatment on their disease but also all possible systemic effects on overall health that can be produced by the applied treatment.

6.1.3 Study Design

Study PEN-03-112

Study PEN-03-112 was a phase III, 84 day (12 week), oral and topical placebo and topical vehicle controlled, double blind, parallel, five arm, multi-center, randomized trial conducted in 38 centers in Canada and 21 centers in US to evaluate efficacy and safety of PENNSAID® in patients with osteoarthritis with moderate knee pain. Seven hundred and seventy five patients were randomized into the five groups (arms) as follows:
1. PENNSAID® + oral diclofenac ("combination" arm)
2. PENNSAID® + oral placebo ("PENNSAID®" arm)
3. Vehicle-control solution (45.5% DMSO) + oral placebo ("vehicle control" arm).
4. Placebo solution (2.3%DMSO) + oral placebo ("placebo" arm).
5. Placebo solution + oral diclofenac ("oral diclofenac" arm).

The administered dose of PENNSAID® was 40 drops 4 times daily applied to the skin surrounding the knee joint. The topical placebo formulation contained 2.3% DMSO to preserve study blinding as discussed above in Section 4.1. All topical formulations were administered at the same dose and regimen (40 drops 4 times daily).

Oral treatment contained either Voltaren XR 100 mg once daily or oral placebo. The patients in the vehicle control arm received a topical formulation similar to PENNSAID® except for its active ingredient, diclofenac sodium.

Only 1 knee, designated as the study knee, was treated with study solution, regardless of symptoms in the other knee. The randomization was stratified according to whether patients had 1 or both knees affected by OA.

The protocol specified treatment duration was 12 weeks (84 days). During the treatment phase there was one telephone 'visit' 1 week after the baseline visit, and 3 more clinic visits at 4, 8 and 12 weeks after the baseline visit. Interim efficacy assessments were performed at weeks 4 and 8 in addition to the final efficacy assessment at week 12.

Prohibited medications:

Screened patients underwent a washout period, up to a maximum of 2 weeks, for discontinuation of prohibited medications/therapies. During the entire study patients were not allowed to take the prohibited therapies. Patients were allowed to take up to four 325 mg acetaminophen tablets per day for rescue relief of pain throughout the study except during three calendar days before efficacy assessments at 4, 8 and 12 weeks. A list of prohibited medications is shown in Table 5 : Following washout, the final entry criterion, flare of pain, was assessed (refer to inclusion criterion #3 below for definition of "flare"). If a patient met the "flare" entry criterion s(he) was considered eligible for the study.

Table 5. List of prohibited medications in study PEN-03-112

Prohibited Medication		Minimum Washout Period Required
NSAIDs	celecoxib, diclofenac, diclofenac with misoprostol, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, mefenamic acid, rofecoxib, tiaprofenic acid, tolmetin sodium, valdecoxib	3 days
	ASA (> 325 mg/day), choline magnesium trisalicylate, naproxen	4 days
	meloxicam, nabumetone	5 days
	oxaprozin	7 days
	piroxicam	10 days
	topical diclofenac	14 days
Muscle Relaxants	e.g. methocarbamol, baclofen, cyclobenzaprine HCl, succinylcholine Cl, dantrolene sodium,cisatracurium besylate, doxacurium, mivacurium Cl, chlordiazepoxide HCl/clidinium Br, rocuronium Br, Norcuron®, diazepam, orphenadrine citrate	3 days
Other Oral Analgesics	acetaminophen, opioids	3 days
Topical Products	methyl salicylate/ camphor/ menthol, capsaicin	3 days
Non-Pharmaceutical Therapy	physiotherapy, massage	3 days
Other Medication	glucosamine, chondroitin, MSM, H_2 blockers, proton pump inhibitors, anti-depressants (MAO inhibitors, tricyclics and SSRIs	7 days

Sponsor's Table 4 (study report # PEN-03-112, p. 29)

Inclusion criteria:

1. Primary OA of the study knee, characterized radiologically by deterioration and abrasion of articular cartilage (joint space narrowing) and/or formation of osteophytes.
Signs of inflammation could be present. The x-ray had to be taken within 3 months (90 days) of the inclusion interview and was interpreted blindly by a central study radiologist, whose report must have confirmed the diagnosis prior to randomization.

2. Symptomatic (painful), primary OA of the knee that required the use of an NSAID or other analgesic on a regular basis (i.e., at least 3 days per week for one month) prior to the screening visit.

3. A 'moderate flare' of knee pain at the baseline assessment, after washout of the regular prior therapy, defined as all of the following:
- a score of at least 2 (moderate) on at least 1 of the 5 items of the baseline WOMAC LK3.1 pain dimension
- an increase in pain dimension total score from screening to baseline of at least 25% and at least 2

- a baseline WOMAC pain dimension total score of at least 8

4. Able to read and understand English well enough to answer the questions in the WOMAC LK3.1 OA Index questionnaire, without any translation.

5. If female:
- The patient could not become pregnant because she was surgically sterile (hysterectomy or tubal ligation), or postmenopausal for at least 6 months OR
- the patient was not pregnant, with a negative pregnancy test at or within 48 hours of the screening visit, and the patient was using an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, spermicide with barrier method, male sexual partner(s) surgically sterile).

6. Signed informed consent form.

7. Between 40 and 85 years of age, inclusive.
8. Except for OA, in reasonably good general health.
9. Able to swallow moderately-sized tablets.

Exclusion Criteria:

1. Secondary OA of the knee (psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma).

2. Clinically significant elevation of serum creatinine (176.8 μmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x ULN).

3. Known sensitivity to the use of diclofenac, DMSO, glycerin, propyleneglycol, ethanol, ASA or any other NSAID.

4. Severe, uncontrolled cardiac, renal, hepatic or other systemic disease.

5. A documented (upper GI series or endoscopy) gastroduodenal ulcer or any GI bleeding (except hemorrhoidal) within six months prior to study enrollment.
NOTE: A patient with documented, active gastroduodenal ulcer disease not associated with NSAID use, with or without bleeding, with evidence of Helicobacter pylori infection (biopsy, urease breath-test or serum antibody) that had subsequently been treated with triple therapy (a seven-day course of a proton pump inhibitor and two of amoxicillin, clarithromycin, or metronidazole) could be included if asymptomatic 90 days after therapy.

6. Documented history of alcohol or drug abuse within one year prior to study entry.

7. Breast-feeding at the time of enrollment.

8. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups. Chondrocalcinosis was allowed if it was an "asymptomatic" radiological finding only.

9. MAJOR SURGERY: Previous damage or surgery to the knee at any time (i.e. damage/reconstruction of the anterior or posterior cruciate ligaments).
MINOR SURGERY defined as anything other than major surgery as defined above less than one year before enrolment.
10. Current treatment with oral or intra-muscular corticosteroids, or intra-articular corticosteroid injection into the study knee within 90 days of study entry or into any other joint within 30 days, or use of topical corticosteroids **at the site of application of the study solution.**
11. Any patient who had received intra-articular viscosupplementation (i.e., Synvisc®) in the study knee 90 days prior to enrollment.
12. Use of prohibited Concomitant Arthritic Medications/Therapies including: any oral NSAID (selective or non-selective), over-the-counter ASA (>325 mg/day), muscle relaxants, other oral analgesics (prescribed or over-the-counter), antidepressants prescribed for the control of chronic pain syndromes, topical products on the knee including methyl salicylate, camphor, menthol, methylsulfonylmethane, DMSO or capsaicin, any non-pharmaceutical therapy or device to relieve knee pain
(including physiotherapy, massage therapy, hot wax therapy etc.).

Glucosamine, chondroitin, and anti-depressants (for indication of depression) were allowed if on stable therapy for 90 days prior to randomization. If in use for fewer than 90 days, these drugs were considered prohibited concomitant medications and required washout.

Patients were allowed to continue stable ASA therapy (up to 325 mg/day) for cardiovascular prophylaxis if already in use for at least 30 days prior to screening.

13. Intolerance to acetaminophen.

14. Any patient who had previously been randomized, applied product and dropped out of this trial was not allowed to re-enter.

15. Use of another investigational drug within 30 days prior to study entry.

16. Any patient on or currently applying for disability benefits on the basis of knee osteoarthritis was excluded.

17. Any patient with fibromyalgia was excluded.

18. Any painful or disabling conditions affecting the knee or leg was excluded.

19. Any patient with a skin disorder with current involvement at the knee(s) was excluded.

20. Any patient who was referred to an orthopedic surgeon for, or advised to have, knee replacement or knee reconstruction surgery was excluded.

21. Any patient who had OA of the knee advanced to the point that all cartilage was eroded, such that on radiological examination the joint space had been eliminated in both lateral and medial tibia/femoral compartments (i.e. bone on bone), was excluded.

Primary endpoints

This study had three co-primary endpoints: changes on WOMAC (Western Ontario and McMaster Universities) OA index's dimensions of pain and physical function and change in Patient Overall Health Assessment Question (POHA) at the 12 week final study visit. The WOMAC Likert 3.1 pain dimension scale consists of 5 questions, each given a weight of 4 points (0-none, 1-mild, 2-moderate, 3-severe, 4-extreme) resulting in a 20 point scale. The WOMAC Likert 3.1 physical function dimension scale consisted of 17 questions each given 4 points weight resulting in a 68 point scale. The POHA question was the following: "Considering all the ways your osteoarthritic (study) knee and its treatment affect you, including both positive and negative effects, how would you rate your overall state of health in the past 48 hours?", with possible answers on a scale of 0-4 (0- very good, 1- good, 2- fair, 3- poor, 4- very poor). The Sponsor pre-specified a clinically important difference as 10% absolute change on each scale.

The primary outcome of the study was comparison of changes from baseline to final study assessment at week 12 in the three co-primary endpoints between the PENNSAID ® group (Group 2) and placebo group (Group 4).

Secondary endpoints
The secondary endpoints in this study were the changes on WOMAC OA index's stiffness dimension at the 12 week final study visit and change in Patient Global Assessment (PGA). The WOMAC stiffness dimension consisted of 2 items assessed on a 0-4 Likert scale. The PGA question was: "How has the OA in your (study) knee been over the past 48 hours", and was assessed on a 0-4 Likert scale.

The major secondary outcomes of this five arm trial were the following:

a. Between-group comparisons of the change from baseline to final study visit of the PENNSAID®/oral placebo arm (Group 2) versus the Vehicle-control/oral placebo (Group 3) for the primary efficacy endpoints

b. Between-group comparisons of the change from baseline to final of the PENNSAID®/ oral placebo arm (Group 2) versus the Vehicle-control/oral placebo (Group 3) and versus Placebo solution/oral placebo (Group 4) for the secondary efficacy endpoints

c. Between-group comparisons of the change from baseline to final of the Vehicle-control /oral placebo (Group 3) versus Placebo solution /oral placebo (Group 4) for all primary and secondary endpoints

d. Between-group comparisons of the change from baseline to final of:
   i. PENNSAID®/oral diclofenac (Group 1) versus the Placebo solution /oral diclofenac (Group 5) for all primary and secondary endpoints,
   ii. PENNSAID®/oral placebo (Group 2) versus the Placebo solution /oral diclofenac (Group 5) for all primary and secondary endpoints.

e. To gain insight into the durability of the response to PENNSAID®:
   i. A comparison of the change from baseline to 4 weeks versus the change from baseline to 8 weeks versus the change from baseline to 12 weeks of the primary and secondary efficacy endpoints for the PENNSAID®/oral placebo arm (Group 2),
   ii. Between group comparisons of the change from baseline to 4 weeks and baseline to 8 weeks of the PENNSAID®/oral placebo arm (Group 2) versus the Vehicle-control/oral placebo (Group 3) and versus Placebo solution/oral placebo (Group 4) for the primary variables

f. Within the PENNSAID®/oral placebo arm (Group 2), assessment of the absolute change from baseline to final for clinical importance. A minimal clinically important difference is defined as a mean change (final minus baseline) score that is at least 10% of the total scale (e.g. for WOMAC Pain, where total dimension scale equals 20, 10% of the scale equals 2)

Pre-specified analysis /sample size calculation

The pre-specified primary efficacy analysis of the study was the comparison between the group of patients treated with topical PENNSAID® and oral placebo (Group 2) and the group of patients treated with topical and oral placebo formulations (Group 4). No adjustment for multiple comparisons was considered for the three co-primary endpoints. The sample size was calculated based on the assumptions of mean differences between the two groups of 1.5 (SD 4.5) in pain and 5 (SD 15) in physical function in absolute numbers on each of the scales (20 for pain and 68 for physical function, respectively). To achieve 80% power with 0.05 two-sided level of significance using ANCOVA test with baseline score as a covariate, it was calculated that 142 patients would be required per group. Assuming a non-evaluable rate of up to 5%, the planned group size was 150 patients, resulting in the total study sample size of 750 patients.
The primary efficacy analysis and all the secondary analyses were performed on the intent-to-treat (ITT) population, defined as all patients randomized and having received at least one single administration of both study drugs (topical and oral). The Sponsor also defined a per-protocol (PP) dataset of patients for a parallel efficacy analysis, which, in general terms, included patients who complied with the protocol, had no major protocol violations, and for whom the primary efficacy measurements were available.

Handling of missing data

For all missing data, the last observation carried forward (LOCF) method was used for imputation for the primary analysis. Additionally, baseline observation carried forward (BOCF) method was used as a form of sensitivity analysis post-blind breaking. BOCF method allows conservative assessment of efficacy while counting the data of patients who dropped out of the study prematurely as unchanged from baseline. This method was appropriately applied in this study.

For missing WOMAC efficacy data where a patient failed to score some questions/items in a given dimension for a given assessment, the average score of the repeated items for that assessment was imputed for the missing item score. This approach was a Sponsor's modification of the approach recommended in the WOMAC User's Guide that stated that such method of imputation was valid only when a minimal amount of missing items had to be imputed. Upon FDA questioning of such approach, the Sponsor provided a Table 6 below, showing the amount of data needed to be imputed by the modified approach, which was minimal for the interim efficacy and non-existent for the final efficacy assessment.

Table 6. Data needed to be imputed for primary efficacy analysis in study PEN-03-112

Visit	Variable	Statistic	Group[2]				
			1 PEN+OD (N=152)	1 PEN+OP (N=154)	3 VC+OP (N=161)	4 P+OP (N=157)	5 P+OD (N=151)
Baseline	Pain	N (%)	0	0	0	0	0
	PF	N (%)	0	0	1 (0.6)	1 (0.6)	0
	Stiffness	N (%)	0	0	0	0	0
4C	Pain	N (%)	0	0	0	0	0
	PF	N (%)	0	0	2 (1.2)	0	1 (0.7)
	Stiffness	N (%)	0	0	0	0	0
8C	Pain	N (%)	1 (0.7)	0	0	0	1 (0.7)
	PF	N (%)	0	2 (1.3)	1 (0.6)	0	0
	Stiffness	N (%)	0	0	0	0	0
Final	Pain	N (%)	0	0	0	0	0
	PF	N (%)	0	0	0	0	0
	Stiffness	N (%)	0	0	0	0	0

Sponsor's Table 2.2.2 (p 12, Response to Clinical Information Request, Sept 18, 2006)
[2] PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Reviewer's discussion of the study design

This study design was planned with the guidance from the Division and was aiming to address several important deficiencies in assessment of efficacy indicated in the second non-approvable

letter issued on August 7, 2002. The following clinically important deficiencies have been indicated in the letter and addressed by the Sponsor:

1. Demonstration of efficacy at the site of application (i.e study knee). "Compassionate" use of the study product, i.e. application of PENNSAID® to both study knee (as indicated) and to the contra-lateral knee (as needed) was allowed in previous studies.

In the design of this study, the study subjects were to apply the topical study formulation to the study knee only and the assessment of primary endpoints was based on the status of the study knee only. The study subject stratification for bilateral and unilateral knee involvement between the groups was also incorporated in this study. Thus, the value of randomization process was assured by treating and counting one knee per randomized subject.

2. Not all randomized and treated patients have been included in the ITT analysis of the previous studies 109 and 109-US performed by the Sponsor. Several such analyses with different imputation methods for missing values were performed by the Division. These analyses showed that depending on the imputation method, the results of the NDA's primary analyses were reversible.

In the current study, the ITT population is defined appropriately and the primary analysis is based on the ITT population with appropriate imputation methods. The BOCF imputation method would allow assessment of the treatment effect without potential bias arising from missing data on patients who prematurely dropped out of the study.

3. No scheduled measurements have been made between baseline and final study assessments in either study 109 or 109-US. Measurements made in the early or the middle stages of a trial are considered important because they provide information about the time course of the drug efficacy, For example, it is important to understand when an effect might begin, and whether this effect is maintained, increased or diminished by the end of study. Future studies should address this issue.

In this study, in addition to the 12 week final study visit time point, the efficacy assessments was performed at 4 and 8 week time points, allowing the assessment of onset and durability of the effect of PENNSAID®.

4. DMSO may be an active component of PENNSAID®.

The current study design includes an arm that contains vehicle control (45.5% DMSO) without the active ingredient, diclofenac sodium, allowing the assessment of efficacy of the 45.5% DMSO and comparison of its effect to those of placebo with negligible amounts of DMSO (2.3%) and PENNSAID®.

For additional information on Sponsor's response refer to section 2.5

Study 109-US

Study 109-US was a phase III, 12 week (84 day), vehicle controlled, double blind, parallel, two arm, multi-center, randomized trial conducted in 40 centers in Canada to evaluate efficacy and safety of PENNSAID® in patients with osteoarthritis with moderate knee pain. Three hundred and twenty six patients were randomized into the two groups (arms) as follows:
1. Topical PENNSAID®
2. Topical Vehicle-control solution (45.5% DMSO)

The administered dose of the study drug was 40 drops 4 times daily applied to the skin surrounding the knee joint.

Treatment of both study knee (according to the study regimen) and the contra-lateral knee (as needed), was allowed during the study. No stratification for bilateral vs unilateral OA knee involvement was done.

The protocol specified a treatment duration of 12 weeks (84 days). Study visits included telephone visits at week 3 and week 9 and clinic visits at week 1, week 6 and week 12 (final visit, at which efficacy assessment was performed).

Screened patients underwent a washout period of 3-10 days, for discontinuation of prohibited medications/therapies prior to the baseline visit at which the patients must have experienced a moderate "flare" of knee pain. The "flare" of knee OA was defined as all of the following:
- Score of at least 2 on at least one of the five items on the WOMAC Likert 3.1 pain dimension subscale
- Baseline WOMAC pain subscale score ≥ 6
- Increase in WOMAC pain subscale score from baseline to screening of 2 points or 25% (whichever is greater).

If both knees were involved and found to qualify for inclusion, the knee with the higher baseline pain score was selected. If the pain scores were the same for both knees, the dominant knee was chosen for the study. Patients were allowed to take up to 4 (four) 325 mg acetaminophen tablets per day for rescue relief of pain throughout the study except during three calendar days before efficacy assessment at week 12.

Inclusion criteria

Inclusion criteria for study 109-US were identical to the inclusion criteria for study PEN-03-112, except the criterion for "flare" of the knee OA, which was defined as above.

Exclusion criteria

Exclusion criteria for this study were identical to the exclusion criteria for study PEN-03-112, except criterion # 2 (see above) specifying baseline laboratory parameters for exclusion from the

study. This criterion was not listed in the Exclusion criteria for the study 109-US since no laboratory assessment was performed at any time during this study.

Primary endpoints
The three co-primary endpoints in this study were: changes on WOMAC (Western Ontario and McMaster Universities) OA index's dimensions of pain and physical function and change in Patient Global Assessment at the 12 week final study visit. WOMAC Likert 3.1 was used in this study similarly to study PEN-03-11.
The primary analysis of the study was comparison of changes from baseline to final study assessment at week 12 in the three co-primary endpoints between the two groups (PENNSAID ® and 45.5% DMSO Vehicle control).

Secondary endpoint
Change on WOMAC OA index's stiffness dimension at 12 week final study visit was the secondary endpoint in this study.

The pre-specified analysis of the secondary endpoint of this trial was a comparison of the change from baseline to final study assessment at week 12 between the two groups (PENNSAID ® and 45.5% DMSO Vehicle control).

Pre-specified analysis /sample size calculation

The pre-specified primary efficacy analysis of the study was the comparison between the two groups for the three co-primary endpoints. No adjustment for multiple comparisons was considered due to prior specification of the three co-primary endpoints. The sample size was calculated based on the assumptions of mean differences between the two groups of 2 (SD 4.5) for pain, 6.8 (SD 15) for physical function, and 0.5 (SD 1.0) for PGA in absolute numbers on each of the scales (maximum of 20 points for pain, 68 points for physical function and 4 points for PGA, respectively). To achieve 80% power with 0.05 two-sided level of significance using ANCOVA test with baseline score as a covariate, it was calculated that up to 80 evaluable patients will be required per group. Assuming a non-evaluable rate of up to 20%, the planned group size was 100 patients, resulting in the total planned sample size of 200 patients.

Study 109-US was originally submitted during the second NDA 20-947 submission in August 2001. The original primary and the secondary efficacy analyses were performed by the Sponsor on the intent-to-treat (ITT) population whose definition differed from that normally applied to studies reviewed by FDA. Thus, according to the original Sponsor's definition, ITT population included all patients who satisfied all major entry criteria, had at least one dose of study medication and had valid baseline and final data. Thus, not all randomized patients were included in the original ITT dataset. During this submission, the Sponsor provided new results after re-analysis of the primary and secondary efficacy endpoints on the correctly defined ITT population (i.e. patients who were randomized, had a baseline assessment and received one dose of the study medication).

Handling of missing data
Missing data were imputed by last observation carried forward method (LOCF). Since in the study 109-US there were only two efficacy assessments recorded (baseline and final) the LOCF method was identical to the baseline observation carried forward (BOCF) in this study.

6.1.4 Efficacy Findings

Study PEN-03-112

Patient Disposition

Study PEN-03-112 randomized 775 patients into five groups as follows:
1. PENNSAID® + oral diclofenac ("combination" arm) -152 patients
2. PENNSAID® + oral placebo ("PENNSAID®" arm) - 154 patients
3. Vehicle control solution (45/5% DMSO) + oral placebo ("vehicle control" arm) – 161 patients
4. Placebo solution (2.3%DMSO) + oral placebo ("placebo" arm) – 157 patients
5. Placebo solution + oral diclofenac ("oral diclofenac" arm) – 151 patients.

Notably, 1 patient in group 1 did not complete any efficacy assessments and 2 patients from group 4 did not receive at least one dose of the study medications (both oral and topical). These three patients were excluded from the study's ITT population.
The patient disposition for study PEN-03-112 is shown in Table 7.

Table 7. Patient disposition in study PEN-03-112

All randomized patients (n=775)	Group 1 PEN+OD (n=152)	Group 2 PEN+OP (n=154)	Group 3 VC+OP (n=161)	Group 4 P+OP (n=157)	Group 5 P+OD (n=151)
Patients who received at least one dose of the study drug (both oral and topical) n (%)	152 (100)	154 (100)	161 (100)	155 (99)	151 (100)
Patients who completed at least one efficacy assessment n (%)	151 (99)	154 (100)	161 (100)	157 (100)	151 (100)
Patients who fulfilled ITT criteria, n=772	151(99)	154(100)	161(100)	155(99)	151(100)
Patients who completed baseline assessments on WOMAC, n (%)					
- pain scale (non-completers -0)	151 (99)	154 (100)	161 (100)	155(99)	151 (100)
- physical function (non-completers-3)	150 (99)	154 (100)	161 (100)	153(97)	151 (100)
- stiffness dimension (non-completers-3)	150 (99)	154 (100)	161 (100)	153(97)	151 (100)
Patients who completed					
- patient Overall Health Assessment Question (non-completers- 8)	148 (97)	154 (100)	160 (99)	152 (97)	150 (99)
- patient global assessment (non-completers-3)	150 (99)	154 (100)	161 (100)	155 (99)	151 (100)
Patients who completed week 12 assessment, n (%)	101(66)	103(67)	113(70)	103(66)	107(71)
Patients who prematurely discontinued, n (%)	51(34)	51(33)	48(30)	54(34)	44(29)
- Adverse event	23(15)	16(10)	12(7)	18(11)	19(12)
- Lack of effect	9(6)	16(10)	17(10)	18(11)	5(3)
- Withdrawal of consent	8(5)	6(4)	10(6)	6(4)	8(5)
- Lost to follow up	2(1)	2(1)	3(2)	4(2)	2(1)
- Death	0	0	0	0	0
- Protocol violation	0	1(1)	1(1)	1(1)	1(1)
- Patient non-compliance	0	1(1)	1(1)	1(1)	0
- Other (scheduling reasons)	9(6)	9(6)	4(2)	6(4)	9(6)

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Approximately two thirds of the patients completed the week 12 assessment with similar drop out rates across study arms. In the PENNSAID® arm (PENNSAID® and oral placebo) the most frequent reasons for drop outs were adverse events (10%) and lack of efficacy (10%). Drop out rates for lack of efficacy were lower in the oral diclofenac arm (Group 5, 3%) and the combination arm (Group 1, 6%). Drop out for adverse events was the highest in the combination arm (15%). Some patients did not complete their baseline assessments for certain mesures, as shown in Table 7 (3- for physical function, 3- for stiffness, 8- for POHA, and 3- for PGA). These patients were excluded from the respective efficacy analyses for particular endpoints. Overall, there were only a minimal number of patients excluded from the secondary analyses. For the primary efficacy comparison, all patients were counted in the PENNSAID® group (Group 2) and only 2-3 patients were excluded from the analyses of physical function, stiffness and POHA in the placebo group (Group 4).

Study Demographics

The baseline patient characteristics were generally similar across the groups (treatment arms), Table 8. The overall patient sample consisted of ~60% females, and ~80 % of patients were

Caucasians with mean age of 62 years. Prior use of medications including NSAIDs, acetaminophen, and topical knee treatments was equally distributed across the groups. There were more patients with depression in the PENNSAID® group at baseline, which explains higher use of psycholeptics as concomitant medications shown in Table 10. None of the study participants were treated and followed in tertiary care study centers. The study sample consisted of patients seen primarily in primary care practice settings.

Table 8. Demographic characteristics of the study participants, study Pen-03-112, ITT population

Variable	Group 1 PEN+OD N=151	Group 2 PEN +OP N=154	Group 3 VC + OC N=161	Group 4 P + OP N=155	Group 5 P + OD N=151
Female gender, (%)	67	68	56	58	63
Race					
Caucasian (%)	77	78	76	77	79
Black (%)	5	7	4	6	4
Asian (%)	5	10	9	13	9
Hispanic (%)	8	4	7	3	7
Other (%)	5	1	4	1	1
Age, mean (SD)	61	62	62	62	62
75 and older, %	10	9	9	10	16
Body weight, kg, Median	86	86	87	86	90
Prior use of NSAIDs (%)	74	74	76	74	74
Prior use of analgesics and other anti-rheumatic drugs (%)	68	58	64	62	60
Prior use of acetaminophen (%)	46	46	37	38	46
Prior use of topical knee treatments (%)	6	3	4	5	6
Patients with depression (%)	7	12	17	8	17
Patients from US/ Patients from Canada(%)	46/54	46/54	46/54	46/54	44/56

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PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

The baseline disease characteristics of the study patients are shown in Table 9. All patients had radiographic evidence of knee OA as was specified in the inclusion criteria. The baseline disease characteristics and the baseline scores of the outcome variables were generally similar across all treatment arms. No information about disease duration and age at the onset of the disease was collected by the Sponsor during the study.

Table 9. Patient disease characteristics, study PEN-03-112, ITT-population

Variable	Group 1 PEN+OD N=151	Group 2 PEN +OP N=154	Group 3 VC + OC N=161	Group 4 P + OP N=155	Group 5 P + OD N=151
Patients with BL knee OA (%)	97	99	96	96	99
Patients with OA of hip or back, n (%)	11 (7)	15 (10)	10 (6)	11 (7)	16 (11)
WOMAC LK3.1					
-pain score, mean(SD)	13(3)	13(3)	13(3)	13(3)	13(3)
-physical function	41(11)	42(13)	41(12)	42(12)	42(12)
-stiffness	5(2)	5(2)	5(2)	5(2)	5(2)
Patient Overall Health Assessment	2.2(1)	2.3 (1)	2.3 (1)	2.2 (1)	2.23(1)
Patient Global Assessment	3 (0.8)	3 (0.8)	3 (0.7)	3 (0.8)	3 (0.9)

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Use of concomitant medications is shown in Table 10. Despite the prohibition of use of a number of medications, many protocol violations were associated with use of such medications. If used, wash out periods were required prior to any efficacy assessments as indicated in Table 5 above in section 6.1.3. The use of anti-inflammatory and anti-rheumatic drugs as well as analgesics appeared to be equally distributed across the groups. The higher percentage of patients receiving psycholeptics and psychoanaleptics in the PENNSAID® group compared to the placebo group is likely explained by higher number of patients with depression randomized to that group (refer to Table 8).

Use of Tylenol was higher in the placebo group (Group 4) when compared with the PENNSAID® group (Group 2) and highest in the Vehicle control group (Group 3). The lowest rates of Tylenol use occurred in the groups with oral diclofenac included as a treatment. Higher use of Tylenol in the placebo group and Vehicle control group suggests two important conclusions. One is that the need for rescue medicine was higher in these two groups when compared with the three other groups, consistent with the ineffectiveness of the treatments. Secondly, because of their use of the rescue medicine, patients in these two groups achieved some degree of pain improvement, tending to bias the results of the efficacy comparison with PENNSAID® toward the null. The greater use of rescue medication then would tend to reduce the magnitude of the difference between the PENNSAID® and placebo groups.

Table 10. Use of concomitant medications in study PEN-03-112, ITT population

Variable	Group 1 PEN+OD N=151	Group 2 PEN +OP N=154	Group 3 VC + OP N=161	Group 4 P + OP N=155	Group 5 P + OD N=151
Tylenol use					
Available ITT population for calculation of number of Tylenol users**	N=143	N=145	N=152	N=141	N=142
Mean (SD) # of capsules per day	0.46(0.7)	0.64 (0.8)	0.99(1.1)	0.95(1.1)	0.55(0.8)
Median # of capsules per day	0.12	0.32	0.52	0.53	0.18
Range # of capsules per day	0-3.8	0.38	0-4.4	0-5.8	0-4.4
Prohibited medication use					
Anti-inflammatory and anti-rheumatic drugs (%)	20	23	35	38	29
Topical products for joint and muscular pain (%)	1	1	2	0	0
Muscle relaxants (%)	1	0	4	1	2
Other drugs for MS system (%)	1	1	0	4	3
Analgesics (%)	53	43	45	48	37
Psycholeptics (%)	11	16	16	10	10
Psychoanaleptics (%)	10	23	24	11	15

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Analysis of Primary and Secondary Endpoints

The primary efficacy analysis was the comparison of the effects of PENNSAID® on the three co-primary endpoints (WOMAC pain, physical function and patient overall health assessment) and the two secondary endpoints (WOMAC stiffness and PGA) with those of placebo (Group 2 vs Group 4).

The important secondary outcomes included:

1. Assessment of the effects of 45.5% DMSO Vehicle-Control treatment (Group 3 vs Group 2 and Group 3 vs Group 4).
2. Assessment of the difference between oral diclofenac alone and the combination of PENNSAID® and oral diclofenac (Group 1 vs Group 5)
3. Assessment of the difference between PENNSAID® and the combination of PENNSAID® and oral diclofenac (Group 2 vs Group 5)

4. Interim efficacy analysis (change in the three co-primary outcomes at week 4 and week 8) for PENNSAID® treated group (Group 2) and comparison with placebo (Group 4) and 45.5% DMSO Vehicle-Control (Group 3); supporting analysis of time weighted average change from baseline to week 12 for WOMAC pain score for group

Table 11 shows the efficacy results for both primary and secondary endpoints for all five study arms in the ITT population.

Table 11. Efficacy analysis across the groups, study PEN-03-112. Mean changes of the scores in five study endpoints after 12 weeks of treatment (ITT, n=772).

Variable	Group 1 PEN+OD N=151	Group 2 PEN+OP N=154	Group 3 VC+OP N=161	Group 4 P+OP N=155	Group 5 P+OD N=151	p-value 2 vs 4	p-value 2 vs 3
WOMAC LK 3.1 pain score ITT population for analysis	N= 151(100)	N=154(100)	N=161(100)	N=155(100)	N=151(100)		
WOMAC LK 3.1 pain score Mean change (SD)	-6.95(4.76)	-6.02(4.54)	-4.70 (4.31)	-4.74(4.35)	-6.43(4.11)	0.0150	0.0094
WOMAC LK 3.1 physical function ITT population for analysis	N=150(99)	N=154(100)	N=161(100)	N=153(97)	N=151(100)		
WOMAC LK 3.1 physical function Mean change (SD)	-18.69 (14.03)	-15.75(15.14)	-12.13(14.58)	-12.34(14.72)	-17.48(14.33)	0.0344	0.0255
Patient Overall Health Assessment ITT population for analysis	N=148(97)	N=154(100)	N=160(99)	N=152 (97)	N=150(99)		
Patient Overall Health Assessment Mean change (SD)	-0.95(1.21)	-0.95(1.30)	-0.65(1.12)	-0.37(1.04)	-0.88(1.31)	<0.0001	0.0158
WOMAC LK 3.1 stiffness ITT population for analysis	N=150(99)	N=154(100)	N=161(100)	153(97)	N=151(100)		
WOMAC LK 3.1 stiffness Mean change (SD)	-2.30(2.00)	-1.93(2.01)	-1.48(2.07)	-1.52(2.05)	-2.07(2.02)	0.1120	0.0347
Patient Global Assessment ITT population for analysis	N=150(99)	N=154(100)	N=161(100)	N=155(99)	N=151(100)		
Patient Global Assessment Mean change (SD)	-1.53(1.27)	-1.36(1.19)	-1.07(1.10)	-1.01(1.18)	-1.42(1.29)	0.0165	0.0181

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

As shown in Table 11, patients treated with PENNSAID® achieved greater relief of pain than patient treated with placebo (6.0 vs 4.7) on the 20 point pain scale (p=0.015). While the magnitude of the change from baseline to the 12 week assessment in each of these groups is considerable, the difference between the groups is ~1.3, demonstrating modest but statistically significant benefit of the PENNSAID® treatment over placebo. PENNSAID® treated patients also achieved a modest, statistically significant benefit compared to placebo-treated patients for the other co-primary endpoints, physical function and patient overall health assessment. With respect to the secondary endpoints, a statistically significant improvement in patient global was observed in the PENNSAID® group and a trend to improvement in stiffness that fell short of statistical significance. The high placebo response observed in this study could, in part, be explained by natural improvement of a moderate disease flare that occurs over time. In summary,

these data indicate a modest but statistically significant benefit for PENNSAID® across the various outcomes measured.

Examination of the results in the Vehicle control arm allows an assessment of the role of DMSO in the clinical activity of PENNSAID®. For the Vehicle control containing 45.5% DMSO, the magnitude of the change in endpoints after 12 weeks of treatment was numerically smaller than that of placebo in all three of the WOMAC dimensions and comparable to placebo in PGA. The improvement in POHA observed in the 45.5 % Vehicle control group compared to placebo is notable; however its significance is unclear. POHA is not a widely used or validated endpoint in OA population; no studies are available for comparison of such response in patients with osteoarthritis of the knee. None of the other well validated variables showed a similar effect, as discussed above. If 45.5% DMSO, in addition to its penetration enhancing properties, truly makes patients feel better, then this beneficial effect likely adds to the treatment effects of PENNSAID®. However, based on the available data from this one study without replication in another study, this beneficial effect can not be either confirmed or refuted. Nonetheless, when the effect on POHA response was compared between patients treated with 45.5% Vehicle control and patients treated with PENNSAID®, modest but statistically significant benefit was seen after treatment with PENNSAID®, when compared to 45.5% DMSO (Group 2 vs 3). These data demonstrate that the presence of topical diclofenac sodium is responsible for the effect on POHA. In the absence of a full factorial design, it is impossible to judge whether this effect of diclofenac sodium is augmented by the presence of 45.5% DMSO.

Comparing Group 2 (PENNSAID® plus oral placebo) to Group 5 (topical placebo and oral diclofenac) and Group 1 (combination of PENNSAID ® and oral diclofenac) allows a comparison between topical diclofenac and oral diclofenac. In general, numerically greater improvement was observed in patients receiving oral diclofenac than those receiving PENNSAID®, but the difference was not statistically significant. Responses to the combination of oral diclofenac and PENNSAID® (Group 5) were in turn somewhat higher then those with oral diclofenac alone, though the differences were also not statistically significant.

Data from the intermediate time points in the trial were examined to assess the time course of clinical benefit associated with PENNSAID® (Table 12). Analysis of the mean changes from baseline to week 4, week 8, and week 12 (final visit) in patients treated with PENNSAID® (Group 2) revealed that the effect of treatment was evident as early as week 4 and was higher than that of placebo at week 12 (5.26 at week 4 with PENNSAID® vs 4.74 at week 12 with placebo).

Table 12. Mean changes in five endpoints observed at different time points in patients treated with PENNSAID®.

Variable	4C minus Baseline	8C minus Baseline	Final minus Baseline
Pain	-5.26 (4.31)	-5.81 (4.42)	-6.02 (4.54)
Physical function	-13.19 (13.06)	-14.75 (14.61)	-15.75 (15.14)
Patient Overall Health Assessment	-0.75 (1.19)	-0.79 (1.29)	-0.95 (1.3)
Stiffness	-1.56 (1.89)	-1.79 (2.01)	-1.93 (2.01)
Patient Global Assessment	-1.13 (1.08)	-1.19 (1.11)	-1.36 (1.19)

Sponsor's Table 6, study PEN-03-112, ISS, p. 21
PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac
4C- clinic visit at 4 weeks
8C- clinic visit at 8 weeks

Analysis of efficacy conducted on the Sponsor's defined "per protocol" dataset demonstrated comparable results and the same magnitude of difference between PENNSAID® and placebo treated groups (Table 13).

Table 13. Efficacy analysis across the groups in study PEN-03-112. Mean changes of the scores in five study endpoints after 12 weeks of treatment (PP, n=562).

Variable	Group 1 PEN+OD N=110	Group 2 PEN+OP N=109	Group 3 VC+OP N=117	Group 4 P+OP N=113	Group 5 P+OD N=113	p-value 2 vs 4	p-value 2 vs 3
WOMAC LK 3.1 pain score PP population for analysis	N= 109	N=109	N=116	N=113	N=113		
WOMAC LK 3.1 pain score Mean change (SD)	-6.86(4.61)	-6.36(4.66)	-5.02(4.36)	-5.02(4.33)	-6.65(4.09)	0.0347	0.0144
WOMAC LK 3.1 physical function PP population for analysis	N=110	N=109	N=117	N=111	N=113		
WOMAC LK 3.1 physical function Mean change (SD)	-18.93(13.98)	-17.31(15.47)	-12.87(14.63)	-13.34(15.27)	-17.83(13.74)	0.0522	0.0144
Patient Overall Health Assessment PP population for analysis	N=106	N=108	N=114	N=106	N=113		
Patient Overall Health Assessment Mean change (SD)	-1.22	-0.98(1.36)	-0.72(1.14)	-0.39(1.16)	-0.93(1.31)	0.0006	0.07
WOMAC LK 3.1 stiffness PP population for analysis	N=110	N=109	N=116	N=111	N=113		
WOMAC LK 3.1 stiffness Mean change (SD)	-2.33(1.99)	-2.08(1.99)	-1.59(2.2)	-1.59(2.13)	-2.06(1.99)	0.1021	0.0278
Patient Global Assessment PP population for analysis	N=110	N=109	N=117	N=111	N=113		
Patient Global Assessment Mean change (SD)	-1.57(1.31)	-1.48(1.28)	-1.20(1.00)	-1.14 (1.16)	-1.51 (1.24)	0.0465	0.0355

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PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Because the patient attrition rate across all arms was ~30%, the analysis of efficacy could be influenced by data from the patients who prematurely dropped out of the study. To assure that the results of the primary efficacy analysis remained consistent regardless of the potential influence of the study dropouts, analysis of dropouts as a group was performed across all study arms. The baseline scores of pain, physical function and POHA of study dropouts did not differ from the baseline scores of ITT population (Table 14). Patients who discontinued from the study prematurely had overall lower responses to any of the administered treatments but did show the same trends in changes from baseline to final. The difference between PENNSAID® and placebo groups (Group 2 vs Group 4) was smaller than that observed in the ITT population, as expected. These data indicate that the data from the drop outs did not bias the overall study results.

Table 14. Primary efficacy analysis of patients who discontinued their study participation prematurely (study PEN-03-112)

Variable	Group 1 PEN+OD N=51	Group 2 PEN+OP N=51	Group 3 VC+OP N=48	Group 4 P+OP N=54	Group 5 P+OD N=44
WOMAC LK 3.1 pain score Mean change (SD)	-5.92	-3.73	-2.13	-2.8	-5.57
WOMAC LK 3.1 physical function Mean change (SD)	-13.63	-7.54	-5.55	-5.62	-16.49
Patient Overall Health Assessment Mean change (SD)	-0.4	-0.47	-0.39	-0.08	-0.55

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

An additional sensitivity analysis was performed with the conservative method of imputation, baseline observation carried forward (BOCF), where all the patients who discontinued prematurely were counted at the final assessment as unchanged from their baseline. The results in this sensitivity analysis were similar to those seen in the primary analysis (Table 15).

Table 15. Efficacy analysis study PEN-03-112 across five arms. Mean changes from baseline to final assessment at 12 weeks.

	Group[1]				
Variable	1 PEN+OD N=151	2 PEN+OP N=154	3 VC+OP N=161	4 P+OP N=155	5 P+OD N=151
Pain	-6.51 (4.87)	-5.81 (4.53)	-4.42 (4.31)	-4.60 (4.33)	-6.11 (4.26)
Physical function	-17.79 (14.24)	-15.05 (15.04)	-11.41 (14.43)	-11.92 (14.70)	-16.59 (14.64)
Patient Overall Health Assessment	-0.91 (1.17)	-0.92 (1.30)	-0.61 (1.11)	-0.35 (1.01)	-0.84 (1.30)

Data from Sponsor's Table 27 (Study PEN-03-112, p. 79)
[1]PEN- PENNSAID®, OP-oral placebo, OD-oral diclofenac, P-topical placebo.

Since the comparison of mean differences per group may not capture the individual patients' changes, the Division requested re-analysis of the data to determine proportion of responders in each study arm according to the pre-specified clinically meaningful difference of 10% absolute change on each scale. Additionally, analysis of responders according to OMERACT-OARSI (Outcome Measures in Rheumatoid Arthritis Clinical Trials – Osteoarthritis Research Symposium International[16-17]) criteria was performed in all study arms, at the request of the Division.

The results of these analyses are shown in the Table 16. Of note, the magnitude of the placebo response is again high and ranges from 38 to 74% across all five endpoints. There are more responders in the PENNSAID® group by 12% in pain dimension, by 13% in physical function,

by 14% in POHA, by 8% in stiffness, and by 18% in PGA. There were 61% moderate or high level OMERACT-OARSI[16-17] responders in the placebo group and 75% moderate or high level OMERACT-OARSI responders in the PENNSAID® group. The difference reached statistical significance for all endpoints, except WOMAC stiffness, where a trend towards more improvement with PENNSAID® was observed.

Table 16. Proportion of responders achieving the pre-specified clinically meaningful difference of 10% absolute change on each scale. Proportion of moderate or high level OMERACT-OARSI responders in each study arm in study PEN-03-112, ITT population

Variable	Group 1 PEN+OD N=151	Group 2 PEN+OP N=154	Group 3 VC+OP N=161	Group 4 P+OP N=155	Group 5 P+OD N=151	p-value 2 vs 4	p-value 3 vs 4
WOMAC LK 3.1 pain score, N (%)	N= 151(100)	N=154(100)	N=161(100)	N=155(100)	N=151(100)		
WOMAC LK 3.1 pain score Responders, n (%)	128(85)	133(86)	120 (74)	114(74)	132(87)	0.005	0.84
WOMAC LK 3.1 physical function, N (%)	N=150(99)	N=154(100)	N=161(100)	N=153(97)	N=151(100)		
WOMAC LK 3.1 physical function Responders, n (%)	117(78)	110 (72)	95 (60)	90 (59)	116 (77)	0.02	0.97
Patient Overall Health Assessment, N (%)	N=148(97)	N=154(100)	N=160(99)	N=152 (97)	N=150(99)		
Patient Overall Health Assessment Responders, n (%)	94 (64)	96 (62)	86 (54)	57 (38)	89 (59)	<0.0001	0.004
WOMAC LK 3.1 stiffness, N (%)	N=150(99)	N=154(100)	N=161(100)	153(97)	N=151(100)		
WOMAC LK 3.1 stiffness Responders, n (%)	119 (79)	110(71)	103 (64)	97 (63)	112 (74)	0.13	0.91
Patient Global Assessment, N (%)	N=150(99)	N=154(100)	N=161(100)	N=155(99)	N=151(100)		
Patient Global Assessment Responders, n (%)	116 (77)	118 (77)	110 (68)	90 (59)	110 (73)	0.0008	0.09
OMERACT-OARSI response, N (%)	N= 151(100)	N=154(100)	N=161(100)	N=155(100)	N=151(100)		
OMERACT-OARSI responders, n (%)	119 (80)	115 (75)	103 (64)	94 (61)	115(76%)	0.008	0.54

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Subgroup Analyses

Subgroup analyses of mean changes across the study arms based on baseline demographics and baseline disease characteristics showed that higher mean changes in scores in all five endpoints were achieved in the PENNSAID® group compared to placebo regardless of age, gender, race, weight, prior or concurrent NSAID use, concurrent use of psycholeptics, psychoanaleptics, prohibited medications such as analgesics, anti-inflammatory and anti-rheumatic drugs, or geographical region (Sponsor's tables# 2.6.1.1 - 2.6.1.5, Submission from September 18, 2006, response to IR letter).

To assess the generalizability of the study results, OMERACT-OARSI moderate and high level responses were analyzed in patient subsets according to the baseline characteristics (Table 17). Higher responses were seen with PENNSAID® than placebo in most subsets with the exception of patients younger than 55 years of age, those weighing less than 80 kg, those taking psycholeptics and those irregularly taking concurrent NSAIDs (prohibited study medications). The significance of these findings is uncertain. They may be artifactual results from multiple post hoc comparisons and small numbers of patients per group.

Table 17. Subgroup Analyses of patients achieving OMERACT-OARSI[16-17] criteria in study PEN-03-112

Category	Sub-category	Group				
		1 PEN+OD	2 PEN+OP	3 VC+OP	4 P+OP	5 P+OD
Gender	Male	N=50 43 (86.0)	N=50 41 (82.0)	N=71 46 (64.8)	N=65 41 (63.1)	N=56 44 (78.6)
	Female	N=101 76 (75.3)	N=104 74 (71.2)	N=90 57 (63.3)	N=90 53 (58.9)	N=95 71 (74.7)
Age, years	35–55	N=54 41 (75.9)	N=38 26 (68.4)	N=37 25 (67.6)	N=46 30 (65.2)	N=41 36 (87.8)
	56–75	N=84 67 (79.8)	N=104 79 (76.0)	N=111 70 (63.1)	N=94 56 (59.6)	N=89 62 (69.7)
	≥ 76	N=13 11 (84.6)	N=12 10 (83.3)	N=13 8 (61.5)	N=15 8 (53.3)	N=21 17 (81.0)
Race	White	N=116 96 (82.8)	N=120 90 (75.0)	N=123 78 (63.4)	N=120 72 (60.0)	N=119 93 (78.2)
	Other	N=35 23 (65.7)	N=34 25 (73.5)	N=38 25 (65.8)	N=35 22 (62.9)	N=32 22 (68.8)
Weight, kg	≤80	N=58 45 (77.6)	N=63 44 (69.8)	N=52 34 (65.4)	N=57 39 (68.4)	N=46 33 (71.7)
	>80 and <90	N=28 22 (78.6)	N=30 26 (86.7)	N=40 25 (62.5)	N=27 16 (59.3)	N=30 21 (70.0)
	≥90	N=64 52 (81.3)	N=61 45 (73.8)	N=69 44 (63.8)	N=71 39 (54.9)	N=74 60 (81.1)
Prior NSAID use	Yes	N=111 88 (79.3)	N=114 83 (72.8)	N=122 75 (61.5)	N=115 68 (59.1)	N=112 85 (75.9)
	No	N=40 31 (77.5)	N=40 32 (80.0)	N=39 28 (71.8)	N=40 26 (65.0)	N=39 30 (76.9)
Concurrent NSAID use	Yes	N=12 11 (91.7)	N=14 9 (64.3)	N=18 10 (55.6)	N=25 16 (64.0)	N=15 12 (80.0)
	No	N=139 108 (77.7)	N=140 106 (75.7)	N=143 93 (65.0)	N=130 78 (60.0)	N=136 103 (75.7)
Concurrent use of psycholeptics and psychoanaleptics	Yes	N=16 11 (68.8)	N=32 22 (68.8)	N=34 21 (61.8)	N=20 12 (60.0)	N=21 18 (85.7)
	No	N=135 108 (80.0)	N=122 93 (76.2)	N=127 82 (64.6)	N=135 82 (60.7)	N=130 97 (74.6)
Concurrent use of anit-inflammatory/ anti-rheumatic drugs	Yes	N=20 17 (85.0)	N=23 16 (69.6)	N=35 18 (51.4)	N=38 22 (57.9)	N=29 21 (72.4)
	No	N=131 102 (77.9)	N=131 99 (75.6)	N=126 85 (67.5)	N=117 72 (61.5)	N=122 94 (77.1)
Concurrent use of analgesics	Yes	N=53 40 (75.5)	N=43 32 (74.4)	N=45 31 (68.9)	N=48 31 (64.6)	N=37 29 (78.4)
	No	N=98 79 (80.6)	N=111 83 (74.8)	N=116 72 (62.1)	N=107 63 (58.9)	N=114 86 (75.4)
Geographical region	US	N=70 53 (75.7)	N=70 52 (74.3)	N=74 48 (64.9)	N=71 43 (60.6)	N=67 57 (85.1)
	Canada	N=81	N=84	N=87	N=84	N=84

		66 (81.5)	63 (75.0)	55 (63.2)	51 (60.7)	58 (69.1)

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

Study 109-US

Study 109-US was reviewed in detail in the previous medical review by Dr. Witter. The most important deficiency, which at the time interfered with interpretation of the study validity, was characterization of the study results based on incorrectly defined ITT population (refer to section 6.1.3 for discussion of the study design). This deficiency prompted the Division's request for re-analysis of the study results on the correctly defined ITT population. This re-analysis was submitted during the current submission and will be reviewed in this efficacy review.

Patient Disposition

In study 109-US, conducted in 43 centers in the USA, 362 patents were randomized into 2 groups: PENNSAID® treated patients (n=164) and 45.5% DMSO Vehicle – control treated patients (n=162). The patient disposition is shown in Table 18.

Table 18. Patient disposition in study RA-CP-109, ITT population

All randomized patients (n=326)	PENNSAID® (n=164)	Vehicle -control (n=162)
Efficacy analysis set (ITT population)	164 (100)	162 (100)
Patients who completed week 12 assessment, n (%)	119(72)	109(67)
Patients who prematurely discontinued, n (%)	**45(38)**	**53(33)**
- Adverse event	8(5)	3(2)
- Death	0	0
- Lack of effect	28(17)	42(26)
- Other (scheduling reasons)	9(5)	7(4)

Study Demographics

The baseline patient characteristics were generally similar between the treatment arms (Table 19). The overall patient sample consisted of ~70% females; ~90 % of patients were Caucasians with mean age of 63-65 years. Almost 80% of patients had bilateral knee involvement. The mean baseline pain score for all study patients was 13 (WOMAC 3.1 Likert 20 point scale). No data were submitted by the Sponsor in regard to the mean OA disease duration for the correctly

defined ITT population. The distribution of prior use of different classes of medications appeared similar between the two groups as shown in Table 19.

Table 19. Demographic and disease characteristics of the study 109-US participants.

Variable	PENNSAID N=164	Vehicle-control N=162
Female gender, (%)	69	67
Race		
Caucasian (%)	87	91
Black (%)	11	7
Asian (%)	1	0
Hispanic (%)	2	1
Other (%)	0	0
Age, mean	63	65
Body weight, kg, Median	92	89
Patients with bilateral knee OA (%)	77	79
Prior use of analgesics (%)	76	82
Prior use of corticosteroids (%)	6	6
Prior use of NSAIDs (%)	15	13
Prior use of topical knee treatments (%)	11	9

Concomitant medications

It is unclear from the available data as to how many patients of the correctly defined ITT population were using prohibited concomitant medications during the study. The mean amount of acetaminophen tablets taken for pain rescue during the study, as reported in Table 55, p. 66 of the original 109-US study report, was 23.7 (range 0-95 tablets) in the PENNSAID® group and 24.5 (range 0-106.6 tablets) in the Vehicle-control group, indicating equal distribution of rescue medication consumed by patients from both groups.

Analysis of Primary and Secondary Endpoints

The primary efficacy analysis was comparison of the effects of PENNSAID® on the three co-primary endpoints WOMAC pain, physical function and patient global assessment with those of 45.5 % vehicle-control.

The secondary outcome was the comparison of the effects of PENNSAID® and 45.5 % vehicle-control on WOMAC stiffness dimension.

Table 20 below shows the mean changes in the scores for all four endpoints in both study arms as well as the proportion of patients classified as moderate or high level responders by OMERACT-OARSI criteria.

Table 20. Efficacy analysis in study RA-CP-109-US. Mean change of the scores from baseline to final visit, comparison between the groups, ITT population, n=326.

Variable	PENNSAID N=164	VC (45.5% DMSO) N=162	p-value
WOMAC LK 3.1 pain score Mean change (SD)	-5.9(4.7)	-4.4 (4.4)	0.0017
WOMAC LK 3.1 physical function Mean change (SD)	-15.3(15.2)	-10.3 (13.9)	0.0024
WOMAC LK 3.1 stiffness Mean change (SD)	-1.8(2.1)	-1.3(2.0)	0.0086
Patient Global Assessment Mean change (SD)	-1.3(1.2)	-1.0(1.1)	0.0052
OMERACT – OARSI responders (moderate or high level)	120/163 (74%)	94/159 (59%)	

As shown in Table 20, the observed effect sizes of both PENNSAID and 45.5% DMSO vehicle control appear to be similar to the effect sizes in study PEN-03-112. The active treatment effect is again modest (1.5 for pain dimension and 5 for physical function dimension) but statistically significantly higher than vehicle control. The effect size of vehicle control is comparable with that of placebo from study PEN-03-112.

Additional controlled trials conducted as part of PENNSAID® clinical development program considered pivotal in previous submissions.

Three additional studies of PENNSAID® were submitted but were not considered pivotal for this review because of their short duration and deficient study designs. Two of these studies demonstrated modest, statistically significant beneficial effects of PENNSAID® over the placebo comparators. One study (#102-93-1) demonstrated a trend towards improvement of knee OA by measuring poorly validated endpoints and did not demonstrate statistical significance. According to the current 21 CFR 314.126 these studies could not be considered adequate and well controlled, therefore the evidence of efficacy originating from these studies is now considered supportive.

Study RA-CP-109

This study was submitted as one of the pivotal studies in the second submission in August 2001. Its design was similar to the design of study 109-US, as it was a double blind, 42 day, 45.5%-DMSO-vehicle controlled, two arm parallel study of safety and efficacy of PENNSAID® in treatment of knee OA conducted in 17 centers in Canada. Two hundred sixteen patients were

randomized into either PENNSAID® (n=107) or 45.5% DMSO vehicle control (n=109) groups. The study population had characteristics similar to those of patients from study 109-US (mean age 65 years, ~60% females, ~90% Caucasians) and was similarly treated with the permission to use the study drug on the contra-lateral knee as needed along with rescue analgesia with acetaminophen 325 mg up to 4 times day. The same deficiency of incorrectly defined ITT population was found in the original analysis of this study, therefore re-analysis on the correct ITT population was re-submitted with the current submission. The study demonstrated a mild beneficial effect of PENNSAID® over vehicle control treatment reaching statistical significance in all three primary study endpoints (WOMAC pain, physical function and PGA), and the secondary endpoint (WOMAC stiffness), similar to that observed in studies PEN-03-112 and RA-CP-109-US. (Table 21). The LOCF imputation method (in this study identical to BOCF since there were only two efficacy assessments) was used for missing data.

Study 107-96

This study was submitted as one of the pivotal studies in the first submission in December 1997. Study 107-96 was a double-blind, randomized, 28 day, placebo- (4.5% DMSO) and Vehicle-controlled (45.5% DMSO) study to evaluate safety and efficacy of PENNSAID® in treatment of knee OA. The primary efficacy endpoint was WOMAC pain score, the secondary efficacy endpoints were WOMAC stiffness, physical function and patient "Daily Global Comparison" (determined as Patient Global Assessment calculated as the sum of weekly scores, not a landmark final minus baseline as in pivotal studies). The study was conducted at 7 centers in Canada and originally called for 150 patients to be enrolled without specification of baseline pain score (non-flare design). During the study it was discovered that "there was some confusion among the investigators about the need for a proper baseline WOMAC scale assessment after washout in those patients using oral NSAID". Subsequently, it was decided to accrue up to 248 patients with the specified baseline pain score (flare design). A post hoc descriptive analysis showed that the mixture of "flare" and "non-flare" resulted in the mean pain score of 9 on the 20 point Likert scale. Patients were allowed to treat the contra-lateral knee as needed and take 650 mg of acetaminophen up to 4 times/day for rescue analgesia. Of the 248 patients, 77 had no recorded baseline pain score. For 48 of these patients (those who were not using NSAIDs or other medications) their screening visit scores were imputed. For the other 29 patients who had been on prior therapy, their Day 1 (on treatment) WOMAC diary scores were imputed. The study demonstrated statistically significantly beneficial effect of PENNSAID® over both placebo and vehicle control.

The effect size of PENNSAID® in comparison with different control treatments from previously submitted four pivotal studies is shown in Table 21. As can be seen, a consistent, moderate beneficial effect of PENNSAID® was observed across the trials.

Table 21. Effect sizes of PENNSAID® when compared with different control treatments across phase III controlled studies (primary analysis of # PEN-03-112, and studies # RA-CP-109-US, #RA-CP-109, #107-96 after re-analysis).

Variable	Study # PEN-03-112 (placebo with 2.3% DMSO)	Study # RA-CP-109-US (45.5% DMSO)	Study #RA-CP-109 (45.5% DMSO)	Study #107-96 (placebo with 4.55% DMSO)	Study #107-96 (45.5% DMSO)
WOMAC LK 3.1 pain score	1.3	1.5	1.9	1.2	1.5
WOMAC LK 3.1 physical function	3.4	5	5.7	4.7	5.9
Patient Overall Health Assessment	0.6				
WOMAC LK 3.1 stiffness	0.4	0.5	0.7	0.9	0.7
Patient Global Assessment	0.4	0.3	0.5	1.2*	1.1*

Between group differences in the primary outcomes across controlled studies: study PEN-03-112 (comparison between PENNSAID plus oral placebo AND topical placebo (DMSO 2.3%) plus oral placebo), study RA-CP-109-US (comparison between the PENNSAID topical solution AND topical 45.5% DMSO vehicle control), study # RA-CP-109 (comparison between the PENNSAID topical solution AND topical 45.5% DMSO vehicle control), study #107-96 (comparison between PENNSAID AND topical placebo containing 4.55 % DMSO and comparison between PENNSAID AND topical 45.5% DMSO vehicle control)
*PGA is calculated as the sum of weekly scores

Study 102-93-1

Study 102-93-1 was a double-blind, randomized, 42 day, placebo- (4.5% DMSO) and Vehicle-controlled (45.5% DMSO) study to evaluate safety and efficacy of PENNSAID® in treatment of knee OA. The primary efficacy endpoints were: patient "Daily Global Comparison score" (determined as Patient Global Assessment calculated as the sum of weekly scores, not a landmark final minus baseline as in pivotal studies) and a total score from the questionnaire that included the following attributes of the study knee: pain and tenderness at rest, pain on motion, joint swelling, joint heat and nocturnal pain. This study failed to demonstrate statistically significant differences between the groups, but showed a trend towards improvement of the above scores in PENNSAID®- treated patients.

Other controlled studies

Study 108-97

Study 108-97 was a double-blind, randomized, 42-day, multi-centered (10 sites in Canada) four arm trial to evaluate safety and efficacy of PENNSAID® in treatment of ——— 203 patients were randomized into four groups: PENNSAID®, placebo- (2.3% DMSO), and Vehicle- control (45.5% DMSO), and topical diclofenac control (1.5% diclofenac sodium and 2.3% DMSO). Enrolled patients had OA of the dominant hand with moderate pain at baseline as assessed by AUSCAN ——————————— The primary efficacy was change in the AUSCAN pain index from baseline to final assessment; change in AUSCAN physical function and stiffness were secondary endpoints. 5-80 drops of PENNSAID® was used depending on the number of ——— involved. Acetaminophen was allowed as a rescue for

b(4)

pain at a dose 500 mg up 6 times daily. One way and two way ANOVA analyses in this study did not reveal statistically significant difference between the study arms for any of the endpoints.

Study PEN-03-110

Study PEN-03-110 was a randomized, double blind, double dummy, 84 day, multi-center (40 centers in Canada), two arm, non-inferiority study comparing efficacy and safety of topical PENNSAID® (50 drops 3 times /day) and oral diclofenac (Voltaren 50 mg three times daily). The primary efficacy endpoints were change from baseline to final on WOMAC pain and physical function dimensions (VAS 0-100) as well as PGA (VAS 0-100), the secondary endpoints were WOMAC stiffness, Overall Health Assessment and overall Quality of Life Assessment. Six hundred twenty-two patients were randomized into either the topical PENNSAID® plus oral placebo group (n=311) or the topical placebo plus oral diclofenac group (n=311). The patient population consisted of 56% females, >90% Caucasians, and the mean age was ~64 years; the baseline characteristics were equally distributed between the groups. Patients were allowed to treat the contra-lateral knee and take acetaminophen for pain rescue. Descriptive data suggested a beneficial effect of oral diclofenac over PENNSAID®. Use of a "per protocol" and not ITT population for the primary efficacy analysis and an improperly defined non-inferiority margin limited interpretability of this study.

6.1.6 Efficacy Conclusions

Analysis of the primary and secondary endpoints of the adequate and well-controlled studies PEN-03-112 and RA-CP-109-US (re-analyzed) provides statistically significant and consistent support for a modest benefit of PENNSAID® in patients with knee osteoarthritis. Subgroup and sensitivity analyses further support the clinical benefits of PENNSAID®. The studies RA-CP-109 and 107-96, although of short duration, additionally provide supportive evidence of the efficacy of PENNSAID® demonstrating a magnitude of effect similar to that observed in the two adequately designed pivotal studies.

Studies PEN-03-112 and RA-CP-109-US provide the principal evidence demonstrating the clinical efficacy of PENNSAID® in the population of patients typically afflicted with primary osteoarthritis, namely elderly and predominantly female patients. Each of the studies used the WOMAC pain and physical function dimensions along with either the Patient Global assessment (RA-CP-109-US) or the Patient Overall Health Assessment (PEN-03-112) as the three co-primary endpoints. Comparison of mean changes from baseline to final study visit demonstrated a modest treatment effect of PENNSAID® over placebo with the following range in the two studies: a 1.3-1.5 point difference on the 0-20 pain subscale, a 3.4- 5 point difference on the 0-68 physical function subscale, a 0.5 points difference on the 0-4 point POHA scale and a 0.3-0.4 points difference on the 0-4 point PGA scale. The predefined difference of at least 10% absolute change from baseline to final study assessment on the each of the scales was achieved with a significantly greater proportion of PENNSAID® treated patients than placebo treated patients achieving this degree of improvement. The proportion of patients achieving OMERACT-OARSI

criteria for moderate or high level response was higher in PENNSAID® treated patients comparing with placebo-treated group (75% vs 61% in PEN-03-112 and 74% vs 59% in RA-CP-109-US).

Efficacy conclusions:

- A modest, statistically significant benefit of PENNSAID® over placebo in treatment of knee OA was demonstrated in the three co-primary endpoints: WOMAC pain and physical function dimensions and PGA
- A modest, statistically significant benefit of PENNSAID® over placebo in treatment of knee OA was demonstrated in the POHA
- For the WOMAC stiffness dimension, a statistically significant modest improvement was demonstrated in study RA-CP-109-US and a trend toward modest improvement was demonstrated in study PEN-03-112
- The improvement in symptoms with 45.5% DMSO was similar and, in some cases, numerically lower than that of placebo (2.3% DMSO)
- The efficacy was lowest in the placebo and vehicle-control groups, statistically significantly higher in the PENNSAID® group, trending to higher efficacy with oral diclofenac treatment, and reaching the highest effect with the combination of PENNSAID® and oral diclofenac
- The effect of PENNSAID in treatment of knee OA was seen as early as 4 weeks and was maintained up to 12 weeks of treatment
- One study of short duration and inadequate design demonstrated no benefit of PENNSAID® treatment in hand OA

Besides those indicated above, there are several other limitations to the interpretation of the available data. First, some important patient disease characteristics were not collected by the Sponsor during the studies (example: mean disease duration for both studies, concomitant medications for study RA-CP-109-US). Knowing this information would have allowed exploration of the potential OA population that would most benefit from the use of PENNSAID®, but lack of this information did not significantly interfere with the interpretation of the efficacy results. Second, the patient sample was comprised mainly of Caucasians, which may make it more difficult to generalize to other ethnicities, although subgroup analysis did not reveal any major differences in the efficacy findings between Caucasians and "other" (all other ethnicities lumped into one group due to small number of patients in each category). Further, "placebo" formulation used in all the studies (including pivotal studies) throughout the development program always contained a small amount of DMSO to preserve study blinding (see section 4.2). Based on the submitted PEN-03-112 study results, the effect of 45.5% DMSO on the symptoms of knee OA was not different from the effect of 2.3% DMSO-containing placebo and numerically and statistically differed from the effect of PENNSAID®. While the lack of a dose effect for DMSO strongly suggests that it has little or no clinical activity, it is still at least theoretically possible that DMSO may have some clinical activity that contributes to the effect of PENNSAID®.

Overall, the data presented in the Sponsor's submission support the claim that PENNSAID® treatment reduces signs and symptoms of primary osteoarthritis of the knee.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of this application, the following safety information was submitted by the Sponsor:

1. Safety data from the seven phase III clinical trials and the extended PEN-03-112E trial included in the development program as presented in Table 4.
2. Case report forms of serious adverse events, deaths, and toxicity related dropouts.
3. A summary of the worldwide experience on the safety of PENNSAID® for the period April 2003 to March 2006, representing spontaneous reports submitted directly to the Sponsor and/or Regulatory Health Agency, primarily from Canadian market where PENNSAID® was approved in March 2003.
4. In response to the Division's request, additional data on DMSO exposure for the whole ISS dataset, re-analyses of the laboratory and vital signs safety data for studies PEN-03-112 and PEN-03-112E, and re-analysis of the ocular adverse events for study PEN-03-112 were submitted by the Sponsor (section 4.1).
5. In response to the Division's request, narratives of the cases of rectal hemorrhages and two cases of retinal detachment from studies PEN-03-112 and PEN-03-112E were submitted by the Sponsor (section 4.1).
6. In response to the Division's request, additional re-analyses of the laboratory and vital signs data for the whole ISS database were submitted by the Sponsor (section 4.1).

This review of safety is organized to separately review the three aspects of safety data:

1. Review of safety data pooled from the seven phase III controlled clinical trials (102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US, RA-CP-110, and PEN-03-112) and presented in six combined arms (PENNSAID® treatment, oral diclofenac treatment, vehicle control treatment, placebo treatment, topical diclofenac control treatment, and combination of oral diclofenac and PENNSAID® treatment). Due to the small number of patients treated with control topical diclofenac, this arm is omitted in some of the tables. From this data, safety of PENNSAID® treatment will be compared with safety of placebo and oral diclofenac treatment.
2. Review of safety data in study PEN-03-112 with specific attention to the safety of the combination treatment (PENNSAID® plus oral diclofenac) in comparison with PENNSAID® treatment alone, placebo treatment and oral diclofenac treatment.
3. Review of safety data in study PEN-03-112E to assess the long term safety of PENNSAID®.

7.1.1 Deaths

Overall, 10 deaths occurred during the PENNSAID® development program. Three deaths occurred in the controlled trials: one patient from phase I sensitization study #101-89-2 received PENNSAID, 45.5% DMSO Vehicle control and placebo (all three treatments) within 22 days and died of cancer of unknown type; one death due to acute myocardial infarction (MI) occurred in a male patient with previous history of HTN and DM who was treated with vehicle - control containing 45.5% DMSO in study #102-93-1. The third patient developed an acute MI while taking oral Diclofenac in study # RA-CP-110, was hospitalized and treated for 3 days and then developed a fatal stroke resulting in death.

There were 7 deaths reported in the long-term studies, the majority were of cardiovascular origin. Four deaths occurred in the open label study #105-95. Three of these were due to acute MI: two of the three patients had cardiovascular risk factors. One death occurred of unknown factors two years after randomization in a patient who was lost to follow up. Three deaths occurred in study # PEN-03-112: 2 acute MIs in patients with previous history of hypertension and coronary artery disease and one death of hypovolemic shock secondary to hematuria in a patient with a previous history of prostate cancer. The majority of cardiovascular deaths occurred in males of 63-84 years of age, which probably reflects the known increased risk for cardiovascular mortality in this population. Overall, no particular pattern to suggest relatedness of the deaths to the study medication was identified from the available data.

Table 22. Listings of deaths for PENNSAID® development program.

STUDY	Patient ID	AGE	GENDER	TREATMENT	TIME	SOURCE	DESCRIPTION
101-89-2	103	45	M	PENNSAID/ 45.5% DMSO/ Placebo	22 days of treatment	101-89-2 study report	Cancer, unclear type, unknown time of development
102-93-1	206	63	M	45.5% DMSO	31 days of treatment	102-93-1study report	Fatal acute MI (previous h/o HTN and DM)
RA-CP-110	21-001	78	M	Oral Diclofenac	During the study	RA-CP-110 Study report	Acute MI, three days of treatment, followed by fatal stroke (previous h/o HTN)
105-95	240	52	F	PENNSAID	6 ½ mo of treatment	ISS	Fatal acute MI (previous h/o CAD)
105-95	1632	71	M	PENNSAID	10 mo of treatment	ISS	Fatal acute MI
105-95	996	65	M	PENNSAID	unknown	ISS	Unknown, patient died 2 years after randomization date
105-95	322	83	M	PENNSAID	unknown	ISS	Fatal MI
PEN-03-112E	05003	72	M	45.5 % DMSO +OP in PEN-03-112, then PENNSAID	3 mo of treatment with VC+OP 4 mo of treatment with PENNSAID	PEN-03-112E Study report	Fatal Coronary thrombosis (previous h/o CAD)
PEN-03-112E	14013	74	M	PENNSAID	10 mo of treatment	PEN-03-112E Study report	Hematuria, hypovolemic shock, un-witnessed cardiac arrest (previous h/o prostatic CA and HTN)
PEN-03-112E	48220	84	M	PENNSAID	2 ¾ mo of treatment	PEN-03-112E Study report	Fatal acute coronary syndrome (prior COPD, HTN)

7.1.2 Other Serious Adverse Events

7.1.2.1. Serious adverse events in controlled phase III trials

A total of 10 out of 911 PENNSAID® treated patients (1%), 5 out of 462 oral diclofenac treated patients (1%), 3 out of 152 patients treated with a combination of PENNSAID® and oral diclofenac (2%), 5 out of 332 of placebo-treated patients (1.5%), and 3 out of 442 vehicle control treated patients (<1%) developed serious adverse events (SAE) during the drug development program (Table 23). Detailed descriptions of all the SAE that occurred in patients treated with PENNSAID® in controlled trials is provided in Appendix A. There were 2 out of 911 cases of coronary thrombosis in PENNSAID®- exposed patients as opposed to 0 out of 332 cases of placebo- exposed patients, and 1 out of 462 oral diclofenac- exposed patients. Cerebrovascular thrombotic events occurred in 2 out of 911 PENNSAID®- exposed patients and in 1 out of 332 placebo- exposed patients. Due to the inequality of the denominators and the small number of cases it is difficult to assess the risk for development of cardiovascular and cerebrovascular events. However, the data suggest that the rate of cardiovascular events with PENNSAID® treatment is higher than that with placebo treatment and similar to that with the approved formulation of orally administered diclofenac sodium treatment. The small number of cases in the submitted data does not allow an assessment of whether the risk with PENNSAID® treatment is lower than that with oral diclofenac treatment.

Table 23. Serious Adverse Events in patients treated with PENNSAID® in seven phase III trials.

TREATMENT GROUP	PENNSAID N=911	ORAL DICLOFENAC N=462	PENNSAID & ORAL DICLOFENAC N=152	PLACEBO N=332	VEHICLE CONTROL N=442
CARDIOVASCULAR	4	1	1	0	1
Coronary thrombosis requiring treatment	2	1	1		
Chest pain requiring evaluation	1				1
Ablative cardiac surgery (planned)	1				
CEREBROVASCULAR	2	0	1	1	1
CVT requiring treatment	2		1	1	
Transient ischemic attack					1
GASTROINTESTINAL		2			1
Upper GI bleeding		1			
Lower GI bleeding		1			
Enteritis					1
ABNORMAL LFTs	0	1	0	0	0
CANCER	1				
INFECTIONS					
Pneumonia				1	
Cellulitis			1		
MUSCULOSKELETAL	1	1	0	2	0
Baker's cyst		1			
Prosthetic hip dislocation				1	
Hip fracture				1	
Right leg and foot pain	1				
ACCIDENTAL INJURY(fall)	1				
ALLERGIC REACTION	1				
ANEMIA				1	

In study PEN-03-112, SAEs were observed only in the combination arm (PENNSAID® plus oral diclofenac) and comprised 1 cardiovascular event, one cerebrovascular event and one cellulitis at the study knee. No SAEs occurred in PENNSAID® only treated patients. Descriptions of serious adverse events that occurred in patients treated in trial PEN-03-112 are presented in Appendix B.

Serious non-fatal adverse events occurring in the uncontrolled trials (including 12 months safety trial PEN-03-112E) are presented in Appendix C. The vast majority of these events were reported from study PEN-03-112E. Only one SAE (case of Crohn's ileitis) was reported in the study 105-95. Study 105-95 was a part of the EDR (Emergency Drug Release) program in Canada (see foot note in Table 4) and was not conducted according to GCP standards, therefore reporting and recording of adverse events including serious adverse events in this study was very limited. In study PEN-03-112E, of the 793 patients who were exposed to PENNSAID®, the following SAE were observed:

- Cardiovascular (5 myocardial infarctions, 5 angina cases)
- Other thrombo-embolic (1 transient ischemic attack, 1 pulmonary embolism)
- Digestive (1 lower GI bleed, 1 upper GI bleed, 1 Partial small bowel obstruction)
- Respiratory (3 cases of pneumonia, 3 cases of COPD exacerbation)
- Musculo-skeletal (3 planned surgeries, 1 Achilles tendon rupture)
- Cancer (1 bladder, 1 breast, 1 stomach)
- Injury (Musculoskeletal-5 cases)
- Genitourinary (1 urinary retention, 1 nephrolithiasis, 1 prostate surgery)
- Psychiatric (1 delusional episode, 1 anxiety attack)
- Allergic (1 case)
- Thrombophlebitis (1 case at the site of study drug application)
- Severe reaction characterized by polyarthralgia, hand arthritis, lip swelling, hives, acute elevation of creatinine to 200μmol (1 case)
- Retinal detachment (1 case of unilateral 70% detachment after 1 month of study drug treatment)
- Syncope (1 case)

All, but one case of myocardial infarction occurred in patients with risk factors predisposing to coronary artery disease (CAD) including HTN, hypercholesterolemia, or previous history of CAD. One patient who had no prior risk factors was a 56 year old male who developed acute MI after 2 ½ months of treatment with the study medication and was continued on the study drug after recovery. Table 24 shows the time of onset of the SAE that occurred in study PEN-03-112E. No particular pattern in occurrence or time of onset of the SAE is observed. The majority of the SAEs occurred in the first 8-9 months of treatment; no increase in SAEs occurred over time. The case of severe reaction with lip swelling, hives, polyarthralgia, and hand arthritis may represent an allergic/hypersensitivity reaction to the study medication. For the incidence of allergic reactions related to PENNSAID® and 45.5 % vehicle control refer to Section 7.1.5. One unexpected SAE in this study was observed, namely retinal detachment. This case is further discussed in Section 7.1.3.

Table 24. Timing of SAEs in uncontrolled trials in PENNSAID®'s development program

TIME (months)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
CARDIOVASCULAR														
Coronary thrombosis requiring treatment	2		1	1	1			1						
Chest pain requiring evaluation					1					1			2	
CEREBROVASCULAR														
Transient ischemic attack		1												
GASTROINTESTINAL														
Upper GI bleeding									1					
Lower GI bleeding			1											
Partial small bowel obstruction	1*													
Crohn's ileitis		1												
MUSCULOSKELETAL														
Achilles tendon rupture		1*												
Bone fracture (post injury)	1***	1					1*							
Right quadriceps tendon tear (post injury)	1													
Polyarthralgia		1												
PULMONARY														
Pneumonia					2			1						
COPD exacerbation								2	1					
Bilateral Pulmonary Embolism									1*					
NEUROLOGIC														
Syncope					1									
PSYCHIATRIC														
Acute Delusional State						1								
Anxiety attack									1***					
UROGENITAL														
Urinary retention	1													
Nephrolithiasis		1												
CANCER														
Bladder				1										
Breast		1***												
Stomach			1											
INFECTIONS														
Total knee replacement (post-surgical infection)			1											
Prosthetic hip infection			1											
Arthroscopic synovectomy (post-procedure infection)					1									
MISCELLANEOUS														
Lip swelling, hives, right wrist arthritis					1									
Painful thrombophlebitis											1			
Retinal detachment	1													

* this patient was enrolled in PEN-03-112E study after participation in PEN-03-112 study and had prior treatment with Vehicle control (45.5% DMSO) in study PEN-03-112

** this patient was enrolled in PEN-03-112E study after participation in PEN-03-112 study and had prior treatment with oral diclofenac in study PEN-03-112

*** this patient was enrolled in PEN-03-112E study after participation in PEN-03-112 study and had prior treatment with the combination of PENNSAID® and oral diclofenac in study PEN-03-112

No SAEs were reported by the Sponsor in their description of the worldwide post-marketing experience presented on pages 51-53, ISS.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall profile of dropouts from all seven phase III controlled trials is shown in Table 25.

The dropout rate across the seven phase III clinical trials ranged from 27% to 35%, lowest in the combined placebo and combined vehicle control arms and highest in the arms with oral diclofenac. Among PENNSAID® treated patients, 10% dropped out due to the lack of efficacy, a similar rate was observed in the placebo group (11%). Fewer patients dropped out from a study if they were treated with either oral diclofenac (3%) or the combination of PENNSAID® and oral diclofenac (6%). The highest dropout rate due to lack of efficacy was observed in the combined vehicle control group, consistent with the lack of efficacy observed with 45.5% DMSO treatment.

To assess the dropout rate due to toxicity, a comparison of the proportion of patients who discontinued the treatment prematurely was made between the combined groups and is shown in Table 25. Among PENNSAID® treated patients ~13% discontinued prematurely due to adverse events compared to ~10% of placebo treated patients. The highest rate of dropout due to toxicity was observed in the oral diclofenac group (~21%), followed by combination group (~15%). The smallest proportion of patients withdrawing for toxicity was observed in the vehicle-control group.

Table 25. Drop out rate in the combined treatment arms across seven controlled trials.

Treatment	No. Exposed	No. (%) Completed	No. Withdrawn		
			Lack of Effect N (%)	Adverse Event N (%)	Other N (%)
PENNSAID®	911	633 (69.5%)	90 (9.9%)	115 (12.6%)	79 (8.7%)
Vehicle-control	603	430 (71.3%)	98(16.3%)	37 (6.1%)	48 (8.0%)
Placebo	332	242 (72.9%)	37 (11.1%)	32 (9.6%)	34 (10.2%)
Oral diclofenac	462	302 (65.4%)	15 (3.2%)	98 (21.2%)	47 (10.2%)
PENNSAID® + oral diclofenac	152	101 (66.4%)	9 (5.9%)	23 (15.1%)	19 (12.5%)
Total	2460	1708 (69.4%)	249 (10.1%)	305 (12.4%)	227 (9.2%)

Data obtained from Sponsor's Table 5, p 18, ISS

In study PEN-03-112, the drop out rate was similar to that observed in the pooled data from the seven trials, about 30% across all five treatment arms (data not shown). The proportion of

patients who discontinued from study PEN-03-112 due to AEs was similar between PENNSAID® and placebo treated patients, but slightly lower in the placebo arm (10% vs 8%). In this study, as opposed to the pooled data, the highest rate of dropout due to toxicity was observed in the combination arm (15%) and the lowest, again, in the vehicle control arm.

In conclusion, similar patient attrition rates due to AEs or lack of effect were observed in the PENNSAID® and placebo arms in Study PEN-03-112 and in the pooled phase III trials data. The highest rate of drop out due to AEs was observed in the arms that included oral diclofenac, likely related to the known toxicity profile of the oral NSAIDs. The lowest rate of drop out due to toxicity and the highest rate of drop out due to lack of efficacy were observed in the vehicle-control arm, consistent with the DMSO component of PENNSAID® serving as a penetration enhancing agent.

In the open-label study PEN-03-112E, 376 out of 795 patients enrolled in the study (47%) discontinued the study prematurely for the reasons described in Table 26. The dropout rate due to toxicity was ~22% in patients treated with PENNSAID® in this 12-month study. This drop out rate is two fold higher than that observed in the controlled trials and was mainly related to application site skin reactions (also see section 7.1.3.2). Although lack of controlled population diminishes the strength of this observation, such relatively high drop out rate indicates that application site skin reactions comprise an important adverse event, that is likely related to PENNSAID® treatment. The AE profile for the dropouts in this study is discussed in the Section 7.1.3.2.

Table 26. Disposition of patients who prematurely discontinued their participation in study PEN-03-112E

Patients randomized, n	795
Patients who prematurely discontinued the study due to AEs	171 (22%)
Discontinued due to insufficient therapeutic effect	96
Lost to follow up	36
Consent withdrawn	31
Non-compliance	10
Deaths	3
Other	29

7.1.3.2 Adverse events associated with dropouts

The overall patient attrition rate due to toxicity in all seven phase III clinical trials in six combined arms is shown in Table 27. The highest proportion of patients who prematurely discontinued their study participation due to AEs were patients who received oral diclofenac, followed by those who received the combination treatment (PENNSAID® and oral diclofenac). Thirteen percent of PENNSAID® treated patients dropped out due to AE compared to ten percent of placebo-treated patients. As shown in Table 27 the most common AEs as a cause of

dropout in PENNSAID® treated patients were application site reactions (56 out of 911 [6%] patients vs 2 out of 332 [<1%] patients treated with placebo), whereas the most common AEs as a cause for dropout in oral diclofenac treated patients were GI related AEs (60 out of 462 patients - 13%). The rate of GI related AEs was higher in the combined PENNSAID® arm compared to the combined placebo arm (3% vs 1%). Drop out due to cardiovascular events was less than 1% in all the groups.

Table 27. Dropouts due to toxicity in seven phase III clinical trials in PENNSAID®'s development program.

Study	Treatment	No. Exposed	Total Patients withdrawing due to AE	Type of Adverse Event (AE)			
				Gastro-intestinal	Application Site Reaction	Other	Cardio-vascular
			N (%)	N (%)	N (%)	N (%)	N (%)
102-93-1	PENNSAID®	41	2 (5)	1 (2)	1 (2)	0	0
	Vehicle control	42	4 (10)	1 (2)	0	2 (5)	1 (2)
	Placebo	39	1 (3)	0	0	1 (3)	0
107-96	PENNSAID®	84	8 (10)	0	4 (5)	4 (4.8)	0
	Vehicle control	80	5 (6)	0	2 (2)	2 (2.5)	1 (1.3)
	Placebo	84	7 (8)	0	0	7 (8.3)	0
108-97	PENNSAID®	50	8 (16)	0	6 (12)	2 (4)	0
	Vehicle control	49	4 (8)	1 (2)	2 (4)	1 (2)	0
	Non-DMSO diclofenac control	52	2 (4)	0	0	2 (4)	0
	Placebo	52	6 (12)	1 (2)	2 (4)	3 (6)	0
RA-CP-109	PENNSAID®	107	9 (8)	0	4 (4)	5 (5)	0
	Vehicle control	109	9 (8)	0	0	8 (7)	1 (1)
RA-CP-109US	**PENNSAID®**	**164**	**8 (5)**	**1 (<1)**	**5 (3)**	**2 (1)**	**0**
	Vehicle control	**162**	**3 (2)**	**1 (<1)**	**0**	**2 (1)**	**0**
RA-CP-110	PENNSAID®	311	64 (21)	18 (6)	31 (10)	15 (5)	0
	Oral diclofenac	311	79 (25)	49 (16)	1 (<1)	27 (9)	2 (<1)
PEN-03-112	**PENNSAID®**	**154**	**16 (10)**	**4 (3)**	**5 (3)**	**6 (4)**	**1 (<1)**
	Vehicle control	**161**	**12 (8)**	**4 (2)**	**2 (1)**	**5 (3)**	**1 (<1)**
	Placebo	**157**	**18 (12)**	**3 (2)**	**0**	**14 (9)**	**1 (<1)**
	Oral diclofenac	**151**	**19 (13)**	**11 (7)**	**0**	**8 (5)**	**0**
	PENNSAID® + oral diclofenac	**152**	**23 (15)**	**6 (4)**	**6 (4)**	**9 (6)**	**2 (1)**
Total	PENNSAID®	911	115 (13)	24 (3)	56 (6)	34 (4)	1 (<1)
	Vehicle control	603	37 (6)	7 (1)	6 (1)	20 (3)	4 (<1)
	Placebo	332	32 (10)	4 (1)	2 (<1)	25 (8)	1 (<1)
	Non-DMSO diclofenac control	52	2 (4)	0	0	2 (4)	0
	Oral diclofenac	462	98 (21)	60 (13)	1 (<1)	35 (8)	2 (<1)
	PENNSAID® + oral diclofenac	152	23 (15)	6 (4)	6 (4)	9 (6)	2 (1)

Data obtained from Sponsor's Table 42, p 63, ISS

Twenty two percent of patients prematurely discontinued their participation in the long term 12-month study PEN-03-112E. The toxicity-related dropout rate for this study is shown in Table 28.

The highest proportion of patients discontinued due to application site reactions (14%). The rates of all other events were 1% or less. No patients discontinued due to non-serious cardiovascular adverse events.

Table 28. Reasons for premature discontinuation of study participation in study PEN-03-112E

Type of adverse event	Patients discontinued from the study due to AE
Total number of patients with AE	171
Serious AE	**13 (8)**
Non-serious AE	**158 (92)**
GI	6 (1)
Application site reaction	114(14)
Other pain/other arthritis	10 (1)
Halitosis, taste perversion, body odor, garlic taste in the mouth	7 (1)
Cardiovascular	0
Elevated LFTs	2 (<1)
Elevated Creatinine	3 (<1)
Ocular AE	5 (<1)
Blurry vision	3 (<1)
Decreased night vision	1 (<1)
Tearing eyes	1 (<1)
Paresthesia	2 (<1)
Other	4 (<1)

7.1.3.3 Other significant adverse events

Two categories of significant AE were identified in association with PENNSAID® in this development program: ophthalmologic AEs (one case of retinal detachment and 18 cases of lens cataracts), as well as rectal hemorrhage (7 cases).

Significant ophthalmologic adverse events

PENNSAID® is a topical product containing 45.5% DMSO that aids dermal penetration of the active ingredient, diclofenac sodium. Some animal studies showed that DMSO given orally and topically was associated with the appearance of lens opacities[2] in dogs and rats. Another study in primate monkeys[4] revealed one case of unilateral retinal detachment, however, the conduct of that study could not exclude a traumatic mechanism for the appearance of retinal detachment in one of the animals. Human studies[6-8] did not reveal any AEs similar to those reported in animals.

Alerted to these possible AEs by the animal data, this review provides a detailed discussion of occurrence of clinical cases of cataracts and retinal and post vitreous detachments in the clinical development program.

Retinal detachment.

Two cases of retinal detachment occurred in the clinical development program. In the controlled trials, no cases of retinal detachment occurred in the PENNSAID® alone treated patients compared to one case of retinal detachment occurring in study PEN-03-110 in the oral diclofenac plus topical placebo arm (2.3% DMSO). In the uncontrolled study PEN-03-112E, one patient developed 70% retinal detachment and was discontinued from the study. The narratives of the cases of retinal detachment were reviewed by the Ophthalmology consultant (Dr. Wiley Chambers). No factors suggesting that the retinal detachment was related to the study drug were identified. Previous history of cataract surgery in that patient may have increased his risk for development of retinal detachment. Overall, no safety signal for the development of retinal detachment was identified in PENNSAID®'s development program.

Cataracts and other ocular events

In the five-arm trial #PEN-03-112, patients underwent ocular examinations at baseline and final visits. A visual acuity test, an assessment of normality for the anterior segment fundus and lens of each eye and a grading of cataract or other opacity (if present) was performed. The incidence and progression of eye disorders in all patients exposed to the study medication are shown in Table 29.

Table 29. Ocular changes occurring in patients in study PEN-03-112

Ocular Parameter Type of Change	Group 1 PEN+OD N=150	2 PEN+OP N=152	3 VC+OP N=156	4 P+OP N=151	5 P+OD N=149
Visual Acuity Lines of Change *	-0.07 (0.49)	0.00 (0.81)	0.01 (0.51)	-0.07 (0.55)	-0.02(0.39)
Anterior Segment Normal to other	7 (5)	8 (5.)	7 (5)	8 (5)	8 (5)
Fundus Normal to other	6 (4)	5 (3)	5 (3)	6 (4)	3 (2)
Lens (Cataract) Normal to other	3 (2)	2 (1)	6 (4)	4 (3)	8 (5)
Cataract severity Increase in severity	6 (4)	6 (4)	12 (8)	12 (8)	17 (11)
Other opacity severity Increase in severity	5 (3)	6 (4)	1 (<1)	5 (3)	8 (5)

Data obtained from Sponsor's table from study report #PEN-03-112, proportions are calculated on the denominator of the exposed patients per group; proportions of patients with ocular changes recalculated on the denominator of patients who completed their eye exams were consistent with the shown data
* lines of change for standard eye chart for best corrected vision, negative change equals an improvement

There were no significant changes in the visual function and appearance or progression of cataracts or new lens opacities in association with treatment with either PENNSAID® or vehicle control (45.5 % DMSO) observed in this trial. However, the interpretability of these data is limited because of the short time of observation (3 months) in view of the natural history of cataract development.

In the seven controlled clinical trials, no definitive pattern of ocular changes was observed in association with treatment with PENNSAID® or vehicle control containing 45.5% DMSO. The following other ocular events listed in Sponsor's Table 18, ISS occurred in <1% of patients treated in the studies: eye infection, eye pain, glaucoma, keratitis, lacrimation disorder, photophobia, visual field defect, retinal degeneration, abnormal vision, blepharitis, corneal lesion, deafness, dry eyes, eye hemorrhage. Conjunctivitis and ear pain each occurred in 2% of patients treated with the non-DMSO containing topical diclofenac control.

In the open label extension study PEN 03-112E, no increase in incidence of blepharitis, dry eyes, conjunctivitis, or lacrimation disorder was observed after 6 and 12 months of treatment with PENNSAID®. There were 18 cases of cataracts reported as adverse events during the 12 month study period (2 were diagnosed in patients who dropped out of the study before 6 month time, 9 were detected at scheduled 6 month visit and 4 were noted between 6 and 12 months). These included 7 new cataracts (6 nuclear and 1 subcortical) in previously normal eyes, and 11 cases of cataract progression (2 cases of progression to the second eye, 5 cases of appearance of a new type of cataract, and 4 cases of increase in severity of the previously diagnosed cataract). Of 793 patients exposed to PENNSAID® in the study, 598 patients completed baseline and final

ophthalmologic evaluations, the total incidence of "cataract" as AE on the denominator of completers was 3% (18/598). The total incidence of new nuclear cataract was 1.2% (6 of 486) of patients who were cataract-free at baseline. The total incidence of new cortical cataract was 0.2% (1 of 486) of patients who were cataract-free at baseline. The total progression rate of nuclear cataract was 2.7% (3 of 112) of patients with cataracts present at baseline, and the total progression rate of cortical cataract was 5.4% (6 of 112) of patients with cataracts present at baseline.

To compare the observed rates with the rates in the general population, the Sponsor conducted a literature search and determined that the observed rates are lower then the rates of appearance and progression of cataracts seen in historical control groups with similar demographic characteristics (Table 30).

Table 30. Comparison of cataract incidence rates in patients treated with PENNSAID® in study PEN-03-112E with the incidence rates of historical controls

Age Range	Incidence Rate in this Study		Rate as per Leske et al.[1,2]		Rate as per Taylor and Munoz[3]	
	Nuclear	Cortical	Nuclear	Cortical	Nuclear	Cortical
<65	1.6%	0.3%	3.4%	4.1%	N/A	N/A
≥65	0.5%	0	10.3%	9.5%	N/A	N/A
Total:	1.2%	0.2%	5.9%	6.5%	11–20%	4%
Age Range	Progression Rate in this Study		Rate as per Leske et al.[1,2]		Rate as per Taylor and Munoz[3]	
<65	0	5.1%	32.6%	10.4%	N/A	N/A
≥65	4.1%	5.5%	37.2%	8.3%	N/A	N/A
Total:	2.7%	5.4%	35.8%	8.9%	14–16%	18–21%

[1]Leske et al., 1996; rates at 2nd year of follow-up
[2] Leske et al., 1997; rates at 2nd year of follow-up
[3]Taylor and Munoz, 1991; rates at one year of follow-up
Data from Sponsor's Tables 24 and 25 pages 54-55, study PEN-03-112E report

Conservatively estimating rates of cataract progression by multiplying the incidence rates in the study by 2 to get an estimate of progression rate by the end of two-year follow up, it appears that the rates of cataract progression in this study were comparable (slightly higher) for cortical cataracts and were lower for nuclear cataracts than the respective rates of historical controls. This comparison taken together with the data from study PEN-03-112 showing no increase in cataract rates in PENNSAID® treated patients compared to placebo-treated patients provides the basis for the conclusion that the overall risk of cataract appearance and progression was not increased with PENNSAID® treatment.

This conclusion, although reasonable in the given circumstances, has some limitations. First, identifying the rates of cataract progression at 1 year of follow up may not reflect the true incidence of cataract appearance that oftentimes is not seen until as late as two years or more of follow up. Second, comparison with historical controls has a limited validity due to the large inter-subject variability. However, the data submitted in this development program do not

suggest a safety signal of increased risk for cataract development associated with PENNSAID® treatment.

A case description of one study participant who developed ocular changes.

One of the participants in the PENNSAID® development program approached the Agency by sending an e-mail to Ombudsman. The patient participated in the double blinded study PEN-03-112 (received oral diclofenac in combination with topical placebo applied to one study knee) and in the open label study PEN-03-112E (received topical PENNSAID® to both knees). It was the patient's understanding that she developed changes in both of her eyes due to the study medication.

A thorough search of the submitted safety datasets was performed and that study participant was identified in the safety datasets in both studies. The subject identification was done based on similarity of the demographic characteristics (age, gender), study center and symptoms associated with ocular changes (decrease in night vision) reported in the person's e-mail. In addition, the subject's initials were identical to those indicated in the e-mail. All the available case report forms (CRFs) for that study subject were reviewed.

The study participant was a 59 y/o female (57 y/o at the time of study participation) with history of diabetes mellitus, hypertension and osteoarthritis. No abnormalities in her eyes were identified at the baseline ocular exam at the time of enrollment to study PEN-03-112. The second and final ophthalmologic exam in study PEN-03-112 after 3 months of treatment with placebo and oral diclofenac showed 1+ nuclear sclerosis in the right eye. The event was correctly coded in the safety dataset (in the cataract variable: change from normal to abnormal) and was included in the final analysis comparing the events between the study arms (Table 29).

The same study participant later enrolled in the open label study PEN-03-112. After six months of treatment with PENNSAID®, she developed decrease in night vision, and at the 26-week study visit an ophthalmologic examination was performed and revealed 1+ nuclear sclerosis in the left eye in addition to the same previous finding in the right eye. The patient discontinued her study participation due to the ocular symptoms, but also related in her e-mail that while using the study solution she experienced pain relief in the osteoarthritic knee within minutes of application. The event of decreased night vision was coded in the safety dataset according to the COSTART as "abnormal vision" and included in the final analysis and AE reporting.

This ophthalmologic history was presented to the Ophthalmology consultant, Dr. Wiley Chambers. It was noted that nuclear sclerosis is a type of cataract, and that most cataracts are part of the normal aging process. Individuals with diabetes usually get cataracts earlier. Nuclear sclerosis is typically graded on a scale 0-4+. Lens change graded as 1+ is considered mild and often does not affect visual acuity. When it does, it mostly increases glare, making it slightly more difficult to see while driving at night. It is usually age related and tends to occur bilaterally, but to a different degree. It is common that the changes are first noticed in one eye and a few months later in the other.

It appears to this reviewer, that occurrence of mild nuclear sclerosis in a 57 y/o woman with a history of diabetes while on placebo treatment for 12 weeks can be explained by other factors, besides study medication. The appearance of mild changes in the contra-lateral eye 6 months later is likely related to the natural history of development of lens changes in this patient, possibly related to her age and the underlying condition. However, a contributory effect of PENNSAID® to development of the mild nuclear sclerosis in the contra-lateral eye can not be excluded.

In conclusion, the data analyses from the studies PEN-03-112 and PEN-03-112E and the individual case review do not reveal any safety signal. However, as indicated above, this conclusion is made with some degree of uncertainty, largely due to the relatively short follow-up periods in both studies and the lack of a control population followed for longer than 3 months.

Significant gastro-intestinal adverse events

Rectal hemorrhages

Six cases of rectal hemorrhages associated with PENNSAID® occurred in study PEN-03-112: five cases occurred in the combination group (PENNSAID® and oral diclofenac) and one case occurred in the PENNSAID® group compared to 0 cases in the other groups in study PEN-03-112. One case occurred in the open label study PEN-03-112E. In the overall development program, in the seven controlled phase III trials, one case of rectal hemorrhage occurred in association with oral diclofenac treatment and one other case occurred in association with placebo treatment (Table 31).

Table 31. Incidence of rectal hemorrhages in PENNSAID® development program

Controlled trials	PENNSAID® N=911	Placebo N=332	Vehicle control N=603	Oral diclofenac N=462	PENNSAID® and oral diclofenac N=152
Rectal hemorrhage, n	1	1	0	1	5

While the overall comparison with placebo and oral diclofenac yields the same rate for occurrence of this AE for PENNSAID® alone treatment in the controlled trials, the increased incidence in the combination group deserves further consideration. The narratives of the cases of rectal hemorrhage that occurred in study PEN-03-112 are shown below.

Group 1 (PENNSAID®+ oral diclofenac):

Rectal Bleeding. *Patient #02023 was a 76 year-old female with a history of irritable bowel syndrome and diverticulosis who was treated with PENNSAID® and oral diclofenac (Group 1)..*

Six weeks after the beginning of the study, the patient reported 'rectal bleeding' which was reported as resolved 4 weeks later. No action was taken and no treatment was administered. The patient continued in the trial until completion on 09/Nov/2004. The investigator assessed this adverse event as moderate.

Rectal Bleeding. *Patient #12023 was a 45 year-old female who was treated with PENNSAID® and oral diclofenac (Group 1) from 14 /Jun/2004. On 30/Jun the patient reported onset of two adverse events, constipation and rectal bleeding. Both adverse events resolved on 08/Jul. No action was taken with study medications and on 06/July the investigator prescribed psyllium hydrophilic mucilloid. The patient completed the trial on 12/Sept/2004. The investigator assessed this adverse event as mild.*

Bleeding hemorrhoid *Patient #12041 was a 50 year-old male who was treated with PENNSAID® and oral diclofenac (Group 1) from 21 /Feb/2005. On16/Apr/2005 the patient began experiencing bleeding hemorrhoids. He was seen in a hospital emergency department and was treated with zinc sulfate monohydrate suppositories. The event resolved by 28/Apr/2005. The patient continued in the trial until completion with no note of further hemorrhoid bleeding. The investigator assessed this adverse event as mild.*

Bleeding hemorrhoid. *Patient #19002 was a 73 year-old female who was being treated with PENNSAID® and oral diclofenac (Group 1) from 03/Apr/2004. Previous to the study this patient had been taking omeprazole for stomach protection (1999 to March 2004). On day 2 of the study the patient began to complain of gastric upset. This event was assessed as moderate and the patient resumed her use of omeprazole the same day. On 27/April the patient began experiencing diarrhea and rectal bleeding from hemorrhoids. That day, the patient discontinued use of the study medications and withdrew from the study. No specific therapy was given and the event resolved by 29/April. The investigator assessed this adverse event as moderate.*

Blood per rectum. *Patient #27050 was a 57 year-old female who was being treated with PENNSAID® and oral diclofenac (Group 1) from 10/Jan/2005. On 27/Jan/2005 she reported blood per rectum, which continued until study completion on 6/Apr/2005. No action was taken and no treatment was administered. The investigator assessed this adverse event as mild.*

Group 2 (PENNSAID® + oral placebo)

Blood per rectum. *Patient #13025 was a 55 year-old male who was being treated with PENNSAID® and oral placebo (Group 2) from 22 /Nov /2004. He had been taking Celebrex® 200 mg OD from 9/Sept/2004 to 11/Nov/2004. On 4/Dec the patient reported "fresh bleeding from anus". This event resolved by 05/December with no action taken and no treatment administered. The patient completed the full 12 weeks of the trial with no further note of anal bleeding. The investigator assessed this adverse event as mild.*

Overall, of the 6 patients with rectal hemorrhages, 5 patients completed their study participation.

As assessed from the descriptions, the case occurring in the patient treated with PENNSAID® and oral placebo was a self-limited case of blood per rectum which did not preclude the patient from study participation and he completed the 12 weeks of the study treatment without any further events. However, this patient had no previous risk factors except prior remote treatment with celebrex and this hemorrhage can probably be related to the study medication.

This isolated case, along with the occurrences in the combined placebo arm (1 case) and in the combined oral diclofenac arm (1 case), suggests a similar risk for rectal hemorrhage with PENNSAID® treatment as with oral dilofenac treatment, but does not allow concluding that the risk was similar to placebo since treatment with oral diclofenac is known to increase the risk of GI hemorrhage compared to placebo.

Of the five other cases in the combination arm, one case of self-limiting hemorrhage occurred in association with constipation and did not preclude continued study participation. Two cases of rectal bleeding occurred in patients with previous history of hemorrhoids. Both events were short-lived and led to discontinuation of study medications in only one of the two patients, in whom hemorrhoids were associated with diarrhea. Two other patients experienced bleeding reported for several weeks to several months, apparently mild and intermittent, and both patients completed their study participation.

Combination treatment with PENNSAID® and oral diclofenac was associated with an increased incidence of mild rectal hemorrhages, especially in patients with a previous history of such predisposing factors as hemorrhoids and diverticulosis. In one case, however, no other risk factors, besides the study treatment, were identified.

In conclusion, based on the available data, treatment with PENNSAID® alone may carry a risk for development of rectal hemorrhage similar to that seen with treatment with the approved formulation of oral diclofenac (Voltaren® XR).

Combination treatment with both topical and oral diclofenac is associated with an increased risk of rectal hemorrhage, especially in patients with other predisposing factors, such as hemorrhoids or diverticulosis.

7.1.4 Other Search Strategies

In PENNSAID®'s development program, no GI hemorrhages (other than rectal hemorrhages) occurred in association with PENNSAID® in controlled clinical trials. Two cases of GI hemorrhage (upper and lower) occurred in the extended open label PEN-03-112E study and were reported as serious AEs. Five cases of melena out of 911 (0.5%) treated patients occurred in PENNSAID® group as opposed to 1 case out of 332 patients in the placebo group, and 8 cases out 462 patients (2%) treated with oral diclofenac.

Review of literature reports on GI hemorrhages related to topical diclofenac products revealed one report[15] of four cases of upper GI hemorrhage in association with treatment with a topical diclofenac formulation- diclofenac gel (Voltaren, Emulgel). In each of these cases patients had other predisposing factors (peptic ulcer disease, H pylori infection, erosive esophagitis). The authors concluded that, as in the case with other NSAIDs, caution should be exercised when prescribing topical diclofenac to patients with history of GI morbidity.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Since the study design in PENNSAID®'s development program varied from earlier to more recent studies, the adverse events were recorded and reported in different ways across the studies. Thus, the adverse events were recorded on a case report form (CRF) by the investigator in studies RA-CP-109, RA-CP-109US, 105-95, RA-CP-110, PEN-03-112 and PEN-03-112E. In the three early studies, 102-93-1, 107-96 and 108-97, patients reported events in a patient diary, which was included in the overall assessment of adverse events in those studies.

In the controlled Phase III clinical trials, 102-93-1, 107-96 and 108-97, adverse events were documented from these sources:
• Patient daily diaries in which patients were to record "any abnormal event you think may be related to the use of the study medication..."
• At each visit, the investigator asked in an open-ended fashion about any adverse events.
• At each clinic visit, the site of application of study solution was assessed and graded for adverse application site reactions, according to a specified standard grading scale (Table 32). Any application site abnormality (i.e., score >0) was considered an adverse event and recorded on a CRF.
• In study 107-96 and 108-96, the investigator asked questions from a checklist of common oral NSAID adverse drug reactions.

In the controlled clinical studies RA-CP-109 and RA-CP-109-US, and open safety study 105-95, the adverse events were documented from these sources:
• At each visit, the investigator asked in an open-ended fashion about any adverse events.
• The investigator asked questions from a checklist of common oral NSAID adverse drug reactions.
• At each clinic visit, the site of application was assessed and graded for adverse application site reactions, according to a specified grading scale (Table). Any application site abnormality (i.e., score >0) was considered an adverse event and recorded on a CRF.

In the controlled clinical study PEN-03-112 and open, long-term safety study PEN-03-112E, there was no checklist of specific NSAID related questions. Adverse events were documented as follows:
• The investigator asked in an open-ended fashion about any adverse events at each visit.

• At each clinic visit, the site of application was assessed and graded according to a specified scoring scale (see Table). Any application site abnormality (i.e., score >0) was considered an adverse event and recorded on a CRF.

In the non-inferiority study RA-CP-110, the adverse events were obtained in four ways:
• The patient volunteered information on AEs and reported it to the investigator during a telephone 'visit' or during a clinic visit.
• At each telephone and clinic visit, the investigator inquired about any AEs, in an open-ended fashion as follows: "Have you experienced any new, unusual event(s) that have not been reported since the last visit or the start of the study?"
• At each clinic visit, the investigator followed the two steps above and then asked questions from a checklist about common AEs of oral NSAIDs.
• At each clinic visit, the investigator assessed the application site for evidence of irritation by the study solution, using a standard grading scale, shown in Table 32.
Any skin irritation score greater than '0' was recorded as an AE and the investigator completed the appropriate AE CRF.

Table 32. Scoring of skin irritation in PENNSAID®'s development program

Score	Study 102-93-1 and 105-95	Study 107-96 and 108-97	Study RA-CP-109, RA-CP-109-US, RA-CP-110, PEN-03-112 and PEN-03-112E
0	no visible reaction	no visible reaction or equivocal response (questionable reaction)	no visible reaction or equivocal response (questionable reaction)
0.5	equivocal response, itching burning sensation, pruritus	itching sensation	dryness or flaking
1	mild erythema	erythema (redness)	erythema (redness)
2	intense erythema	erythema and induration (i.e. swelling)	erythema with induration (*i.e.*, swelling)
3	intense erythema with edema	erythema with induration and vesiculation (small blisters ≤ 5 mm)	erythema with induration and vesiculation (*i.e.*, small blisters ≤5 mm)
4	intense erythema with edema and vesicular erosion	erthyema with induration and bullae (large blisters > 5 mm)	erythema with induration and bullae (*i.e.*, large blisters >5 mm)

Sponsor's Table 15, ISS, p 29.

All safety assessments performed in phase III controlled clinical trials are summarized in Table 33.

Table 33. Safety evaluations in PENNSAID®'s development program

Study	Irritation Assessment	Skin Sensitization Assessment	AE Evaluation				Vital Sign Evaluation	Clinical Lab Evaluation[3]	Ocular Visual Examination
			Diary Documentation	CRF Documentation	Safety Self-Assessment[1]	NSAID AE Checklist[2]			
102-93-1	X	X	X	X			X	X	
107-96	X	X	X	X				X	
108-97	X		X	X		X	X		
RA-CP-109	X			X		X	X		
RA-CP-109-US	X			X		X	X		
RA-CP-110	X			X	X	X	X	X	
PEN-03-112	X			X			X	X	X

[1] Patient self-assessment in regards to oral NSAID-related symptoms
[2] Investigator queries of patient in regards to oral NSAID-related symptoms
Sponsor's Table 3.0.1from IR submitted September 18, 2006

The adverse event reporting and recording, although varied across the studies, was adequate. Of all the controlled phase III studies and uncontrolled trials, the best designed and conducted were the more recent studies # PEN-03-112 and # PEN-03-112E. This safety review will examine both the pooled data across all the trials and the safety data and the rates of most common adverse events in these two studies separately. The safety assessment of the pooled data will be done by comparison of AE rates in the five combined arms that include all the patients exposed to a particular treatment (PENNSAID®, placebo, oral diclofenac, 45.5% DMSO, vehicle control, and combination of PENNSAID® and oral diclofenac). To assess the safety of the combination arm, study PEN-03-112 will be reviewed separately. To assess the long term safety of PENNSAID® treatment, study PEN-03-112E will also be reviewed.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Safety of PENNSAID® was assessed by analyzing all adverse event reports. The Sponsor coded each adverse event according to the COSTART dictionary (U.S. Food and Drug Administration, 1995) throughout the development program. All the adverse events describing dropouts in study PEN-03-112 were described by the investigators' terms focusing on the events occurring that led to discontinuation of the study treatment (Table 27).

7.1.5.3 Incidence of common adverse events

Section 7.1.5.4 discusses in detail the incidence of common AEs in the seven phase III controlled trials as well as presents the common AEs tables.

7.1.5.4 Common adverse event tables

In this development program, in seven phase III clinical trials, application site skin reaction was the most common adverse event occurring in patients treated with PENNSAID® compared to placebo (32% vs 5% for dry skin and 9% vs 2% for contact dermatitis, 4% vs 2% for pruritis). Paresthesia at the application site occurred at equal rates in PENNSAID® and placebo treated patients. Gastro-intestinal adverse events occurred at a higher rate in PENNSAID® treated patients as compared to placebo with the following frequency (dyspepsia-8% vs 4%, abdominal pain-6% vs 3%, flatulence- 4% vs <1%, diarrhea- 4% vs 1%, nausea-4% vs 1%, constipation-3% vs <1%). Edema and peripheral edema occurred in a higher proportion of patients treated with PENNSAID® compared to placebo (3% vs 0 and 1% vs <1%, respectively). Infections, rash, ecchymosis, pruritis, and paresthesia occurred at a slightly higher rate with PENNSAID® than with placebo (Table 34). Notably, taste perversion occurred at equal rates in PENNSAID®, placebo, and Vehicle control combined arms (3%), whereas halitosis occurred at a slightly higher rate in the PENNSAID® arm, compared to placebo and all other arms, however, still in a small proportion of patients (1% vs <1% or 0).

Comparing the incidence of AEs between the combined PENNSAID® arm and the oral diclofenac arm or the combination (PENNSAID® and oral diclofenac) arm allows comparison between the AE rates of oral and topical diclofenac. Thus, GI related events occur at higher rates in the oral diclofenac combined arm (dyspepsia-19%, abdominal pain-17%, flatulence- 11%, diarrhea- 13%, nausea-10%, constipation- 7%). Edema also occurs at higher rate with oral diclofenac compared to PENNSAID® (6% vs 3%). The AE profile of the combination group does not show any increase in the rate of AE over that seen in oral diclenac or PENNSAID®, except the incidence of severe cases of contact dermatitis that are seen in the highest proportion in the combination group compared to PENNSAID® and placebo (4% vs 2% vs 0).

Table 34. Most common AEs that occurred in ≥1% patients, treated with PENNSAID®.

Treatment Group:	PENNSAID® N=911	Placebo N=332	Vehicle-control N=603	Oral diclofenac N=462	PENNSAID® and Oral diclofenac N=152
	N (%)	N (%)	N (%)	N (%)	N (%)
Dry Skin (Application Site)	292 (32)	17 (5)	123 (20)	8 (2)	30 (20)
Arthralgia	102 (11)	80 (24)	97 (16)	26 (6)	7(5)
Headache	95 (10)	65 (20)	81 (13)	46 (10)	21(14)
Contact Dermatitis (Application Site)	83 (9)	6 (2)	25 (4)	6 (1)	12(8)
Dyspepsia	72 (8)	13 (4)	23 (4)	87 (19)	5(3)
Abdominal Pain	54 (6)	10 (3)	10 (2)	78 (17)	3(2)
Back Pain	51 (6)	23 (7)	39 (7)	14 (3)	4(3)
Pain	49 (5)	25 (8)	41 (7)	17 (4)	1(<1)
Pharyngitis	40 (4)	13 (4)	12 (2)	4 (1)	0
Paresthesia (Application Site)	37 (4)	19 (6)	36 (6)	2 (<1)	1(<1)
Flatulence	35 (4)	1 (<1)	2 (<1)	52 (11)	0
Pruritus (Application Site)	34 (4)	7 (2)	20 (3)	2 (<1)	1(<1)
Diarrhea	33 (4)	7 (2)	8 (1)	61 (13)	12 (8)
Nausea	33 (4)	3 (1)	10 (2)	44 (10)	5(3)
Constipation	29 (3)	1 (<1)	4 (<1)	33 (7)	2(1)
Edema	26 (3)	0	4 (<1)	27 (6)	4(3)
Peripheral edema	8(1)	2(<1)	4(<1)	1(<1)	0
Infection	25 (3)	8 (2)	11 (2)	18 (4)	1(<1)
Rash	25 (3)	5 (2)	12 (2)	7 (2)	0
Flu Syndrome	24 (3)	9 (3)	19 (3)	5 (1)	2(1)
Joint Disorder	23 (3)	29 (9)	25 (4)	3 (<1)	0
Taste Perversion	23 (3)	9 (3)	16 (3)	2 (<1)	1(<1)
Accidental Injury	22 (2)	7 (2)	14 (2)	11 (2)	6(4)
Arthrosis	21 (2)	26 (8)	16 (3)	4 (1)	0
Ecchymosis	19 (2)	1 (<1)	6 (1)	9 (2)	2(1)
Dry Skin	19 (2)	1 (<1)	5 (<1)	1 (<1)	2(1)
Contact Dermatitis, vesicles (Application Site)	18 (2)	0	0	1 (<1)	6(4)
Asthenia	16 (2)	6 (2)	9 (2)	4 (1)	1(<1)
Pruritus	15 (2)	2 (<1)	10 (2)	10 (2)	0
Paresthesia	14 (2)	3 (1)	11 (2)	4 (1)	1(<1)
Rhinitis	13 (1)	7 (2)	11 (2)	7 (2)	1(<1)
Halitosis	11 (1)	1 (<1)	5 (<1)	1 (<1)	0
Application Site Reaction	11(1)	3 (1)	5 (<1)	0	0
Dizziness	10 (1)	5 (2)	6 (1)	13 (3)	3(2)
Cough Increased	10 (1)	5 (2)	11 (2)	7 (2)	0
Sinusitis	10 (1)	2 (<1)	4 (<1)	6 (1)	3(2)

[1]Studies 102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US, RA-CP-110 and PEN-03-112. Events occurring in ≥1% PENNSAID® patients shown only; presented in decreasing order of frequency.

Source: Sponsor's Table 18 from ISS p 119, Table 20 from ISS, p 36

To examine the safety of 45.5% DMSO, the AE occurring in ≥ 1% patients treated with vehicle control were examined. Apart from those listed in Table 34, two other AEs were observed in ≥ 1% patients treated with vehicle control: bronchitis and neck pain. Bronchitis occurred in 14 out of 603 (2%) patients treated with 45.5% DMSO compared to 3/332 (1%) placebo- treated patients and 8/911 (<1%) PENNSAID®- treated patients. Neck pain occurred in 12/462 (2%) of 45.5% DMSO treated patients but was observed in the same proportion of placebo-treated patients 6/332 (2%) and less in PENNSAID® treated patients- 8/911(<1%).

Allergic reaction occurred in 5 out 911 patients with PENNSAID® and 3 out of 603 patients treated with vehicle control.

In conclusion, across the pooled data from the seven phase III trials, application site dermatological reactions were the most common AEs seen in patients treated with PENNSAID®. GI- related events and edema occurred in higher proportions of patients with PENNSAID® compared to placebo, but in lower proportions of patients treated with PENNSAID® compared to oral diclofenac. No increase in AEs was seen in the combination group except the higher proportion of severe skin reactions at the application site.

To further examine the AE profile of PENNSAID®, the results from the adequately designed and well controlled study PEN-03-112 were explored in detail.

The most common AEs occurring in ≥ 5% patients treated with PENNSAID are listed in Table 35. Higher rates of back pain and headache were observed with PENNSAID® as compared to placebo (10% vs 6% and 18% vs 12%). Overall pain occurred in a slightly higher proportion of PENNSAID® treated patients as compared to placebo. The rate of back pain was lower in the arms that included oral diclofenac (7% in Group 5 and 3 % in Group 1). The observed variability in occurrence of these symptoms may be attributed to the variability in efficacy of the selected treatments in achieving improvement in musculoskeletal and overall pain.

With respect to GI –related events, the rate of diarrhea was lower with PENNSAID® compared to placebo and oral diclofenac alone, and highest in the combination group (8%). Liver function test abnormalities occurred at a higher frequency in PENNSAID® compared to placebo (2% vs 0.6%), but occurred at the highest rates in the oral diclofenac arms (8% and 7%).

Application site reactions were high in the PENNSAID® group compared to placebo in study PEN-03-112, similar to the finding observed in the pooled data (18% vs 3% for dry skin, and 2.6% vs 0.6% for contact dermatitis). The highest proportion of cases with dry skin reactions and contact dermatitis occurred in the combination arm.

Thus, the increased proportion of liver abnormalities and the highest rate of severe skin events suggest a safety concern associated with the combination therapy of PENNSAID® and oral diclofenac (see section 7.1.7.3.1).

Table 35. The most common AE occurred in ≥ 5% patients in study PEN-03-112

Body system*	Preferred term	Group 1 PEN+OD	Group 2 PEN+OP	Group 3 VC+OP	Group 4 P+OP	Group 5 P+OD
		N=152	N=154	N=161	N=157	N=151
Body as a whole	Abdominal pain	3 (2.0)	5 (3.2)	5 (3.1)	1 (0.6)	11 (7.3)
	Back pain	4 (2.6)	15 (9.7)	15 (9.3)	10 (6.4)	11 (7.3)
	Headache	21 (13.8)	27 (17.5)	21 (13.0)	18 (11.5)	26 (17.2)
	Pain	1 (0.7)	7 (4.5)	11 (6.8)	5 (3.2)	8 (5.3)
Digestive	Diarrhea	12 (7.9)	2 (1.3)	2 (1.2)	3 (1.9)	7 (4.6)
	Liver function tests abnormal	11 (7.2)	3 (1.9)	6 (3.7)	1 (0.6)	12 (7.9)
Musculoskeletal	Arthralgia	7 (4.6)	14 (9.1)	25 (15.5)	15 (9.6)	12 (7.9)
Skin and appendages	Dry skin, application site	30 (19.7)	28 (18.2)	18 (11.2)	5 (3.2)	4 (2.6)
	Contact dermatitis, application site	12 (7.9)	4 (2.6)	5 (3.1)	1 (0.6)	1 (0.7)

*From Sponsor's Table 31, p 91, and Table 14.3.39 from the study report # PEN-03-112

To further characterize the AE profile of PENNSAID® and explore the AE profile of the combination of PENNSAID® and oral diclofenac, the AEs observed in <5% but ≥ 2 % of patients treated in study PEN-03-112 were examined (data not shown). Rectal hemorrhage occurred in 5 out of 152 patients (3%) treated with the combination of PENNSAID® and oral diclofenac and in 1 out of 154 patients treated with PENNSAID® compared to 0 cases in the placebo group in this study (refer to section 7.1.3.1 for detailed discussion of this AE). Nausea occurred in 3% of patients treated with the combination of PENNSAID® and oral diclofenac but no cases were seen in PENNSAID®- or placebo- treated patients.

To assess the occurrence of AEs associated with long-term use of PENNSAID®, the rate of AEs occurring in ≥ 1% of patients was examined in the open label 12-month study PEN-03-112E. The most common AEs occurring in this study are shown in Table 36.

Table 36. Common AEs occurring in ≥1 % patients treated with PENNSAID® in study PEN-03-112E

Preferred Term	All patients N=793*
Body as a whole	**N (%)**
Accidental injury	41 (5)
Back pain	28 (4)
Headache	30 (4)
Pain	21 (3)
Abdominal pain	18(2)
Chest pain	14(2)
Edema	9(1)
Flu syndrome	16(2)
Halitosis	18(2)
Infection	17(2)
Allergic reaction	9(1)
Chest pain	14(2)
Leg pain	10(1)
Cardiovascular	
Hypertension	28 (4)
Peripheral edema	11 (<2)
Digestive	
Liver function tests abnormal	31 (4)
Diarrhea	11(<2)
Dispepsia	11(1)
GI disorder	13(<2)
Vomiting	5(<1)
Hemic and lymphatic	
Ecchymosis	8 (1)
Metabolic & nutritional	
Creatinine increased	19(2)
Hyperglycemia	4(<1)
Hypokalemia	4(<1)
Musculoskeletal	
Arthralgia	63 (8)
Arthritis	14(2)
Joint disorder	7(<1)
Nervous	
Paresthesia	14(2)
Paresthesia at appl site	3(<1)
Insomnia	9 (1)
Respiratory	
Bronchitis	29 (4)
Respiratory disorder	49 (6)
Cough increased	13(2)
Pharyngitis	14(2)
Rhinitis	8(1)
Sinusitis	11(<2)
Skin & appendages	
Contact dermatitis,	103 (13)

application site	
Contact dermatitis with	75 (10)
vesicles, application site	
Dry skin, application site	201 (25)
Dry skin	18(2)
Pruritis, apll site	8(1)
Rash	33(4)
Skin nodule	4(<1)
Special senses	
Abnormal vision	22(3)
Blepharitis	13(<2)
Dry eyes	11(1)
Lacrimation disorder	9(1)
Cataract	18(2)
Conjunctivitis	8(1)
Eye disorder	12(2)
Taste perversion	8(1)
Urogenital	
Urinary tract infection	15(2)
Hematuria	8(1)

795 patients were enrolled in the study, but
793 patients were exposed to the study drug
Data obtianed from Sponsor's Table 14.3.20, Study PEN-03-112E report

The frequency of skin reactions was 25% in the open label study with contact dermatitis occurring in 13% and contact dermatitis with vesicles in 10% of patients. Cataracts were observed in 2% of patients (detailed discussion see in section 7.1.3.1). Hypertension occurred in 28 out of 793 patients exposed to PENNSAID® (see detailed discussion in section 7.1.8).

7.1.5.5 Identifying common and drug-related adverse events

Adverse reactions that occurred in greater frequency than 1% in the PENNSAID® group are described in section 7.1.5.1. The AEs that were more common in the PENNSAID® group than in placebo group are shown in Table 37.

It can be clearly seen that application site reactions appeared at higher frequency in groups whose treatment included either PENNSAID® or vehicle control, with the most severe reactions (contact dermatitis with vesicles) occurring in the combination (PENNSAID® plus oral diclofenac) group (4%). This reviewer concludes that the application site reactions were likely related to PENNSAID® and its topical application.

GI and renal adverse effects observed with systemic NSAIDs were also observed in association with treatment with topical diclofenac sodium. However, the rate of these AEs was lower with topical as compared to oral diclofenac sodium. Thus, in patients treated with PENNSAID®, symptoms of GI irritation (dyspepsia, abdominal pain, flatulence, diarrhea, nausea, and constipation) occurred more frequently than in patients treated with placebo, but less frequently

than in patients treated with either oral diclofenac or the combination of oral and topical diclofenac.

Edema and peripheral edema were more frequent in the PENNSAID® group then in the placebo group, with edema occurring at the highest incidence in the oral diclofenac group. Occurrence of infection, rash, ecchymosis, pruritus, paresthesia, and sinusitis was slightly higher (by 1%) in the PENNSAID® group than in the placebo group.

Interestingly, while taste perversion occurred at equal rates in the PENNSAID®, placebo, and vehicle control treated group (possibly related to the presence of DMSO in placebo formulations), the incidence of halitosis, although small (1%), still exceeded that of placebo and vehicle control.

Table 37. Drug related AEs in PENNSAID®'s development program

Treatment Group:	PENNSAID® N=911	Placebo N=332	Vehicle-control N=603	Oral diclofenac N=462	PENNSAID® and Oral diclofenac N=152
	N (%)	N (%)	N (%)	N (%)	N (%)
Dry Skin (Application Site)	292 (32)	17 (5)	123 (20)	8 (2)	30 (20)
Contact Dermatitis (Application Site)	83 (9)	6 (2)	25 (4)	6 (1)	12(8)
Dyspepsia	72 (8)	13 (4)	23 (4)	87 (19)	5(3)
Abdominal Pain	54 (6)	10 (3)	10 (2)	78 (17)	3(2)
Flatulence	35 (4)	1 (<1)	2 (<1)	52 (11)	0
Pruritus (Application Site)	34 (4)	7 (2)	20 (3)	2 (<1)	1(<1)
Diarrhea	33 (4)	7 (2)	8 (1)	61 (13)	12 (8)
Nausea	33 (4)	3 (1)	10 (2)	44 (10)	5(3)
Constipation	29 (3)	1 (<1)	4 (<1)	33 (7)	2(1)
Edema	26 (3)	0	4 (<1)	27 (6)	4(3)
Peripheral edema	8(1)	2(<1)	4(<1)	1(<1)	0
Infection	25 (3)	8 (2)	11 (2)	18 (4)	1(<1)
Rash	25 (3)	5 (2)	12 (2)	7 (2)	0
Taste Perversion	23 (3)	9 (3)	16 (3)	2 (<1)	1(<1)
Ecchymosis	19 (2)	1 (<1)	6 (1)	9 (2)	2(1)
Dry Skin	19 (2)	1 (<1)	5 (<1)	1 (<1)	2(1)
Contact Dermatitis, vesicles (Application Site)	18 (2)	0	0	1 (<1)	6(4)
Pruritus	15 (2)	2 (<1)	10 (2)	10 (2)	0
Paresthesia	14 (2)	3 (1)	11 (2)	4 (1)	1(<1)
Halitosis	11 (1)	1 (<1)	5 (<1)	1 (<1)	0
Sinusitis	10 (1)	2 (<1)	4 (<1)	6 (1)	3(2)

[1]Studies 102-93-1, 107-96, 108-97, RA-CP-109, RA-CP-109-US, RA-CP-110 and PEN-03-112. Events occurring in ≥1% PENNSAID® patients; presented in decreasing order of frequency.

Source: Sponsor's Table 18 from ISS p 119, Table 20 from ISS, p 36

7.1.5.6 Additional analyses and explorations

As expected, application skin reactions were the most common AEs related to PENNSAID® and its route of administration. Analysis of the application site dermatological reactions was performed in phase I studies (100-89, 101-89-2, 103-93-2, 104-93-3) and described in the previous dermatology review by Dr. Hon-Sum Ko. The degree of skin irritation was assessed in phase III clinical trials (see full descriptions of the skin scores in Table 32). Analysis of skin irritation scores in phase III controlled trials is shown in Table 38.

As shown in Table 38, ~31% of patients treated with PENNSAID® developed skin irritation with the majority (22%) represented by skin dryness. Skin erythema occurred in 5% of patients treated with PENNSAID® as compared to 1% in the placebo, 3% in the vehicle control and 2% in the topical diclofenac control groups. The highest rate of severe skin reactions occurred in the combination group where 7% of patients developed erythema and 4% of patients developed contact dermatitis with vesicles. According to the Sponsor's statement (p 30, ISS), the skin irritation was reversible in all cases.

Table 38. Skin irritation scores in phase clinical trials

Irritation Scores in Phase III Controlled Clinical Studies

Skin Irritation Score2	PENNSAID® N=904	Placebo N=328	Vehicle-control N=600	'Non-DMSO' diclofenac control-3 N=51	Oral diclofenac N=461	PENNSAID® + Oral diclofenac N=152
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
0	627 (69)	302 (92)	483 (80)	38 (74)	440 (95)	103 (68)
0.5 (equivocal response or dryness)	196 (22)	20 (6)	96 (16)	11 (22)	11 (2)	30 (20)
1 (erythema)	48 (5)	4 (1)	19 (3)	1 (2)	9 (2)	11 (7)
2 (erythema and induration)	7 (<1)	2 (<1)	2 (<1)	1 (2)	0	1(<1)
3 (2 + vesicles)	25 (3)	0	0	0	1 (<1)	6 (4)
4 (2 + bullae)	1 (<1)	0	0	0	0	0

Data obtained from Sponsor's Table 16, p 30, ISS.

Application site reactions observed in controlled phase III clinical trials are shown in Table 39.

Application site reactions coded as AEs were seen in 52% of patients treated with PENNSAID® (32%- dry skin), 16% of patients treated with placebo (5% -dry skin), 34% of patients treated with 45.5% DMSO (20%-dry skin), 44% of patients treated with topical diclofenac sodium (23% dry skin), and 33% of patients treated with the combination of oral and topical diclofenac (20%-dry skin). Only 4% of patients treated with oral diclofenac and topical placebo developed application site reactions (dry skin 2%).

It is likely that the skin dryness can be attributed to both topical diclofenac and topical DMSO, resulting in the increased rates of dry skin with PENNSAID® treatment.

Occurrence of contact dermatitis in the PENNSAID® arm exceeded placebo by 7% (9% vs 2%). The rates of contact dermatitis at the application site were comparable in the topical diclofenac alone and the combination arms (8% in each). Two percent of patients developed contact dermatitis with vesicles in the PENNSAID® treated group compared to none in the placebo group and 4% in the combination group. The rates of pruritus and urticaria were slightly higher in the PENNSAID® arm comparing to placebo.

Table 39. Application site reactions in the phase III clinical trials

Treatment group	PENNSAID® N=911	Placebo N=332	Vehicle-control N=603	"Non-DMSO" diclofenac control N=52	Oral diclofenac N=462	PENNSAID® + oral Diclofenac N=152
Vasodilation (app site), N(%)	5 (<1)	4(1)	4(<1)	1(2)	0	0
Paresthesia (app site)	37 (4)	19(6)	36 (6)	4(8)	2(<1)	1(<1)
Acne (app site)	1(<1)	0	0	0	0	0
Contact Dermatitis (app site)	83(9)	6(2)	25(4)	4(8)	6(1)	12(8)
Contact Dermatitis, vesicles (app site)	18(2)	0	0	0	1(<1)	6(4)
Dry skin (app site)	292(32)	17(5)	123 (20)	12(23)	8(2)	30(20)
Pruritis (app site)	34 (4)	7(2)	20 (3)	2(4)	2(<1)	1 (<1)
Urticaria (app site)	1(<1)	0	0	0	1(<1)	0

Data obtained from Table 18, ISS

The time of onset of the skin reactions was assessed in the long term study PEN-03-112E. Table 40 shows that the rate of the application skin reactions did not increase over time.

Table 40. Application site reactions occurring over time in study PEN-03-112E

	TIME				
	0-13 weeks N=746	14-26 weeks N=580	27-39 weeks N=448	40-52 weeks, N=230	53-65 weeks, N=116
Contact dermatitis, application site	43 (5.8)	44 (7.6)	21 (4.7)	8 (3.5)	1 (0.9)
Contact dermatitis with vesicles, application site	29 (3.9)	34 (5.9)	5 (1.1)	7 (3.0)	0 (0.0)
Dry skin, application site	117 (15.7)	51 (8.8)	20 (4.5)	12 (5.2)	3 (2.6)

Overall, high rates of application site reactions were associated with PENNSAID® but the majority of these reactions were comprised of skin dryness. The events of contact dermatitis were generally reversible upon drug discontinuation.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In this development program, laboratory parameters were collected in 4 phase III trials: 102-93-1(6 week study), 107-96 (4 week study), RA-CP-110 (12 week study), and PEN-03-112 (12 week study). In each of these trials the laboratory parameters were obtained at baseline and final visits. In addition, laboratory parameters were measured at 4 week time point in study PEN-03-112.

The clinical laboratory parameters measured in each study are shown in Table 41.

Table 41. Laboratory parameters measured in PENNSAID®'s clinical development program.

Laboratory Parameter	Study			
	102-93-1	107-96	RA-CP-110	PEN-03-112
[redacted]				
Hemoglobin	X	X	X	X
Hematocrit	X	X		X
Platelets	X	X	X	X
Erythrocytes				X
WBC	X	X	X	X
Granulocytes	X	X		
Lymphocytes	X	X	X	X
Monocytes	X	X	X	X
Eosinophils	X	X	X	X
Neutrophils			X	X
Basophils	X	X	X	X
Bands				X
[redacted]				
Sodium	X	X	X	X
Potassium	X	X	X	X
Chloride	X	X	X	X
Bicarbonate			X	X
Albumin	X	X		
Total Protein	X	X		
Glucose	X	X		
Urea	X	X	X	X
Creatinine	X	X	X	X
Creatinine Clearance			X	X
Uric Acid	X	X		
Bilirubin	X	X		X
AST	X	X	X	X
ALT	X	X	X	X
GGT			X	X
Alkaline Phosphatase	X	X		
Lactic Acid Dehydrogenase	X			
[redacted]				
Protein	X	X	X	X
Blood	X	X	X	X
Leukocytes		X	X	X
Glucose	X			X
Ketones				X
Bilirubin				X
Urobilinogen				X
Nitrite				X
pH	X			X
Specific Gravity	X			X

WBC		X	X	
RBC		X	X	
Cast (hyaline)		X	X	
Cast (granular)		X	X	

Data obtained from Sponsor's Table 3.0.2 (ISS, Info Request response submitted Sept 18, 2006)

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

To assess changes in laboratory parameters, the data were pooled from all four trials where the laboratory tests were obtained (102-93-1, 107-96, RA-CP-110, and PEN-03-112).

Laboratory changes were assessed in the five combined arms at the following time points: baseline to 4 weeks, baseline to 6 weeks and baseline to 12 weeks. Since the vast majority of patients had their assessment of laboratory parameters at 4 and 12 weeks, these data will be presented in this review. No differences were observed between changes in laboratory parameters at 4 and 6 week assessments. Since not all the enrolled patients had all the laboratory tests performed, and the tests measured varied from study to study, results of each test will be presented with the respective number of patients in whom this particular test was obtained.

Sponsor's original definition of clinically significantly abnormal (CSA) change in laboratory values is shown in Table 42.

Table 42. Sponsor's original definition of clinically significantly abnormal (CSA) laboratory values.

Parameter	Reference (Normal) Range	Clinically Significant Abnormality
Hematology		
Hemoglobin (g/L)	M:135–170 F: 115–155	M: ≤ 115 F: ≤95
Hematocrit (L/L)	M: 0.38–0.49 F: 0.33–0.45	Not defined
Erythrocytes ($x10^{12}$/L)	M: 4.20–5.70 F: 3.60–5.01	Not defined
Platelets ($x10^9$/L)	145–400	≤75 or ≥ 700
Leukocytes ($x10^9$/L)	4.0–11.0	≤2.8 or ≥ 16
Neutrophils ($x10^9$/L)	1.8–7.0	≤0.9
Lymphocytes ($x10^9$/L)	1.0–3.2	Not defined
Monocytes ($x10^9$/L)	0.0–0.8	Not defined
Eosinophils ($x10^9$/L)	0.0–0.4	≥0.6
Basophils ($x10^9$/L)	0.0–0.2	Not defined
Bands ($x10^9$/L)	0.0–1.0	Not defined
Blood and Liver Chemistry		
Sodium (mmol/L)	135–145	10% below LLN or 10% above ULN
Potassium (mmol/L)	3.3–5.1	10% below LLN or 10% above ULN
Chloride (mmol/L)	95–108	10% below LLN or 10% above ULN
Bicarbonate (mmol/L)	20–30	10% below LLN or 10% above ULN
Bilirubin Total (µmol/L)	<17	≥2 x ULN
Bilirubin Direct (µmol/L)	<5	Not defined
Urea (mmol/L)	2.5–8.1	≥ 11
Creatinine (µmol/L)	M: 60–110 F: 50–100	≥ 176.8
Creatinine Clearance (mL/min)[1]	M: 97–137 F: 88–128	Not defined
AST (U/L)	M : <37 F : <31	≥3 x ULN
ALT (U/L)	M : <46 F : <36	≥3 x ULN
GGT (U/L)	M : <60 F : <36	≥3 x ULN
Urinalysis		
Protein (g/L)	< 0.3	Increase of ≥ 2 units
Blood	Negative	Increase of ≥ 2 units
Leukocytes	Negative	Increase of ≥ 2 units
Glucose (mmol/L)	Negative	Not defined
Ketones (mmol/L)	Negative	Not defined
Bilirubin	Negative	Not defined
Urobilinogen (µmol/L)	3.2–16	Not defined
Nitrite	Negative	Not defined
pH	5.0–8.0	Not defined
Specific Gravity	1.005–1.030	Not defined
Source of CSA values: Appendix III of the protocol		

[1]estimated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976). Normal range, source: http://www.nlm.nih.gov/medlineplus/ency/article/003611.htm [accessed February 16, 2006]

Sponsor's Table 38 (p 108, PEN-03-112 study report, also ISS)

The Division considered this definition adequate for capturing any markedly abnormal changes in the laboratory parameters but not adequate for capturing any clinically significantly abnormal changes that would typically be considered worrisome in clinical practice. Therefore, a re-analysis of the CSA values based on revised definitions of CSA was requested by the Division. Although the specific cut offs chosen are still arbitrary, these newly defined CSA values permit a better assessment of any changes that would be considered clinically abnormal in medical practice.

The criteria for newly defined CSA are shown below:

- hemoglobin - ≤100 g/L for females and ≤115 g/L for males
- platelet count - ≤ 100 or ≥ 500 x 109/L
- WBC - ≤ 3.5 or ≥ 13.0 x 109/L
- Sodium ≤ 130 or ≥ 150 mmol/L
- Potassium ≤ 3.1 or ≥5.5 mmol/L
- Chloride ≤ 91 or ≥110 mmol/L
- Bicarbonate ≤ 18 or ≥ 32 mmol/L
- Urea ≤ 9.3 mmol/L

The values of the measured liver enzymes, bilirubin and creatinine ranging 1.5UNL-3UNL were considered the newly defined CSA as opposed to the previously defined CSA of ≥3UNL for these parameters.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The mean changes in the serum laboratory tests obtained in this development program are shown in Table 43.

No significant or clinically meaningful difference was observed in the group mean change in PENNSAID® treated patients compared to placebo in any of the laboratory parameters. Notably, more decrease in hemoglobin occurred at 4 weeks of treatment with PENNSAID® , compared to placebo, but this change disappeared by 12 weeks of treatment. A mild, clinically insignificant, drop in platelets was observed in the PENNSAID® group compared to placebo. A small decrease in GGT at 4 weeks in the PENNSAID® group disappeared at 12 weeks; other liver function tests did not change significantly and remained in a range comparable with placebo. Renal function and electrolytes changed slightly and no more than in placebo-treated patients.

No significant change occurred in urine pH or specific gravity in any of the arms or in any other parameters in urinalysis (changes concerning the presence of blood in urine were insignificant and are shown in Table 46).

Examination of the oral diclofenac arm and the combination arm data allowed assessment of changes in laboratory parameters in these two groups and a comparison with PENNSAID®. As shown in Table 43, a decrease in hemoglobin was observed in the oral diclofenac group comparing to PENNSAID® at both 4 and 12 weeks of treatment. However, the most significant decrease in hemoglobin occurred in the combination group, suggesting augmentation of the toxicity of oral diclofenac by addition of the topical diclofenac sodium. Changes in liver function tests were also more pronounced in the oral diclofenac arm comparing with PENNSAID®. The combination group showed results comparable with oral diclofenac. With respect to renal function, a more significant increase in creatinine was observed in the oral diclofenac arm in comparison with PENNSAID®, but the highest change again occurred in the combination (PENNSAID® and oral diclofenac) arm.

Table 43. Mean changes in laboratory parameters in PENNSAID®'s development program

Parameter	Treatment				
	PENNSAID	Placebo	Vehicle Control	Oral Diclofenac	PENNSAID + Oral Diclofenac
Hemoglobin (g/L)					
Number of patients	N=207	N=197	N=195	N=122	N=124
4 weeks	-2	-1	-0.3	-3.2	-3.4
Number of patients	N=419	N=142	N=151	N=411	N=143
12 weeks	-0.01	-0.9	-0.4	-2.7	-4.8
WBC(X10E6/L)					
Number of patients	N=207	N=197	N=195	N=122	N=124
4 weeks	-0.1	-0.2	-0.3	-0.1	-0.2
Number of patients	N=413	N=142	N=151	N=410	N=143
12 weeks	-0.2	-0.05	-0.06	-0.3	-0.07
Platelets (X10E9/L)					
Number of patients	N=202	N=190	N=191	N=120	N=120
4 weeks	-2	2	0.02	-3	-0.3
Number of patients	N=417	N=138	N=148	N=408	N=142
12 weeks	-4.6	2	3	1	4
AST (U/L)					
Number of patients	N=207	N=197	N=191	N=122	N=123
4 weeks	-0.4	-0.2	0.4	2.7	2.8
Number of patients	N=425	N=142	N=150	N=414	N=141
12 weeks	-0.1	-0.6	0.2	4.6	4
ALT (U/L)					
Number of patients	N=205	N=195	N=195	N=122	N=123
4 weeks	0.2	-0.2	-0.3	6	7
Number of patients	N=425	N=142	N=150	N=414	N=141
12 weeks	0.4	-0.3	-0.6	12	8
GGT (U/L)					
Number of patients	N=125	N=122	N=121	N=122	N=123
4 weeks	-3	3	0.3	5	2
Number of patients	N=425	N=142	N=150	N=415	N=142
12 weeks	2	2	-1	11	0.3
Bilirubin, total (umol/L)					
Number of patients	N=207	N=196	N=193	N=122	N=123
4 weeks	-0.01	0.15	0.1	-0.02	-0.3
Number of patients	N=146	N=142	N=150	N=139	N=142
12 weeks	0.1	-0.2	-0.1	-0.2	-0.3
Creatinine (µmol/L)					
Number of patients	N=207	N=195	N=193	N=122	N=123
4 weeks	0.2	1	1	2	5.7
Number of patients	N=426	N=142	N=150	N=415	N=141

12 weeks	0.06	0.7	0.28	3.2	4.4
Urea (mmol/L)					
Number of patients	N=204	N=194	N=193	N=122	N=123
4 weeks	0.1	-0.1	-0.05	0.7	0.7
Number of patients	N=420	N=142	N=150	N=413	N=142
12 weeks	0.02	-0.1	-0.2	0.5	0.5
Sodium (mmol/L)					
Number of patients	N=207	N=197	N=194	N=122	N=123
4 weeks	-0.2	0.01	-0.2	0.1	-0.05
Number of patients	N=425	N=142	N=150	N=415	N=142
12 weeks	-0.5	-0.2	-0.1	-0.1	0.3
Potassium (mmol/L)					
Number of patients	N=207	N=197	N=194	N=122	N=123
4 weeks	-0.04	-0.02	0.07	0.03	0.02
Number of patients	N=426	N=142	N=150	N=415	N=142
12 weeks	-0.03	0	-0.04	0.02	0.03
Chloride (mmol/L)					
Number of patients	N=207	N=197	N=194	N=122	N=123
4 weeks	0.3	0.01	0.03	0.5	0.8
Number of patients	N=424	N=142	N=150	N=415	N=142
12 weeks	-0.1	-0.1	0.1	0.2	1
Bicarbonate (mmol/L)					
Number of patients	N=125	N=122	N=121	N=122	N=123
4 weeks	-0.1	-0.4	-0.3	0.1	-0.3
Number of patients	N=414	N=142	N=150	N=413	N=142
12 weeks	0.5	0.1	0.2	0.5	-0.2

Data obtained from Source Tables 3.1.1, 3.1.2, and 3.1.3 ISS provided by Sponsor in submission September 18, 2006

To assess the mean changes in the laboratory parameters with more precision while paying special attention to the combination arm, the mean changes in the study PEN-03-112 were examined and are summarized in Table 44. In general, the same trends in changes in the laboratory parameters as the trends derived from the pooled data were observed in this study. However, with regard to the liver function tests, they increased slightly more with PENNSAID® treatment comparing to placebo, and more so in the oral diclofenac group. Contrary to the results from the pooled data, the increase in LFTs in this study was most pronounced in the combination group, again suggesting augmentation of the liver toxicity associated with oral diclofenac by adding the topical diclofenac formulation.

Table 44. Mean changes in laboratory parameters occurring in study PEN-03-112

Lab Parameter *	Group				
	PEN+OD Group 1	PEN+OP Group 2	VC+OP Group 3	P+OP Group 4	P+OD Group 5
Hemoglobin	N=143	N=145	N=151	N=142	N=138
g/L	-4.80 (6.79)	-1.68 (6.22)	-0.38 (6.53)	-0.85 (6.23)	-3.79 (7.09)
Creatinine	N=141	N=145	N=150	N=142	N=138
umol/L	4.41 (11.21)	-0.41 (10.50)	0.28 (10.33)	0.76 (8.98)	3.13 (11.00)
Creatinine	N=140	N=144	N=149	N=141	N=138
Clearance, mL/min	-3.28 (9.69)	0.42 (10.29)	-0.47 (8.29)	-0.48 (8.59)	-2.41 (8.70)
AST	N=141	N=145	N=150	N=142	N=138
U/L	4.07 (29.56)	-0.86 (10.28)	0.22 (8.49)	-0.56 (5.15)	2.51 (10.89)
ALT	N=141	N=145	N=150	N=142	N=138
U/L	8.21 (68.93)	-1.04 (11.73)	-0.57 (9.84)	-0.31 (9.88)	7.23 (25.30)
GGT	N=142	N=146	N=150	N=142	N=139
U/L	0.27 (28.69)	-0.58 (14.23)	-1.09 (13.46)	1.92 (21.05)	4.81 (17.58)

*This table is based on the Sponsor's data from Table 39, page 109; PEN-03-112 study report
The values in the cells represent means per group of patients in whom the indicated parameters were measured. The values in the parentheses represent standard deviations of the corresponding means.

The changes in the mean laboratory data occurring over time are shown in Table 45. No increases in mean laboratory parameters were observed with prolonged treatment with PENNSAID® up to 12 months.

Table 45. Mean changes in laboratory parameters occurring over time in study PEN-03-112E

Parameter	TIME				
	Baseline	Week 14	Week 26	Week 40	Week 52/ Final All patients*
Hemoglobin (g/L)	N=779	N=533	N=347	N=170	N=696
Mean	142	140	140	140	141
WBC(X10E6/L)	N=778	N=533	N=347	N=170	N=697
Mean	6.8	6.8	6.8	6.8	6.8
Platelets (X10E9/L)	N=774	N=525	N=343	N=166	N=687
Mean	258	262	265	267	264
AST (U/L)	N=778	N=534	N=347	N=171	N=695
Mean	22	22	22	22	23
ALT (U/L)	N=778	N=534	N=347	N=170	N=694
Mean	23	24	23	23	23
GGT (U/L)	N=779	N=534	N=347	N=171	N=695
Mean	32	30	30	30	31
Bilirubin (umol/L)	N=779	N=534	N=347	N=171	N=695
Mean	8	8	8	9	8
Creatinine (µmol/L)	N=778	N = 534	N=347	N=171	N=696
Mean	77 (18)	77 (17)	78 (16)	77 (16)	80 (19)
Creatinine Clearance (mL/min)	N=770	N=529	N=345	N=170	N=689
Mean	73	72	70	70	70
Median	72	69	68	67	68
Urea (mmol/L)	N=779	N=534	N=347	N=170	N=694
Mean	6	6	6	6	6
Sodium (mmol/L)	N=778	N=534	N=347	N=170	N=694
Mean	141	140	140	141	140
Potassium (mmol/L)	N=779	N=534	N=347	N=171	N=695
Mean	4	4	4	4	4
Chloride (mmol/L)	N=779	N=534	N=347	N=171	N=695
Mean	103	103	103	103	103
Bicarbonate (mmol/L)	N=778	N=534	N=347	N=171	N=695
Mean	24	24	24	24	24

Data obtaitned from Source Tables 14.3.44, 14.3.45 provided by Sponsor in study PEN-03-112E
*all patients at their final study visit regardless of duration of study participation

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

In the controlled clinical trials, laboratory parameters were measured at baseline and final visits in studies 102-93-1(6 week study), 107-96 (4 week study), RA-CP-110 (12 week study), and PEN-03-112 (12 week study). In addition, laboratory parameters were measured at the 4 week time point in study PEN-03-112. Table 46 below represents the pooled data from the 4 studies showing the proportions of patients with changes in laboratory values from normal to any abnormal. As indicated above in section 7.1.7.2 , the Division disagreed with the Sponsor's definition of clinically significantly abnormal (CSA) change in the laboratory values and requested re-analysis of the data according to the new definition of CSA. Table 46 shows change from normal to any abnormal, from normal to previously defined CSA, and from normal to newly defined CSA.

Table 46. Changes in laboratory parameters from normal to abnormal, from normal to clinically significantly abnormal (newly defined CSA) and from normal to markedly abnormal (previously defined CSA) in PENNSAID®'s development program.

Laboratory value*	PENNSAID®	Placebo	Vehicle-control	Oral diclofenac	PENNSAID® + Oral diclofenac
Hemoglobin, n (%)	N=539	N=256	N=261	N=420	N=147
Abnormal	16 (3)	12 (5)	13 (5)	38 (9)	19 (13)
Newly defined CSA	2(<1)	1 (<1)	1(<1)	3 (<1)	0
Previously defined CSA	1 (<1)	0	0	3 (<1)	0
Platelets	N=540	N=253	N=262	N=420	N=147
Abnormal	6 (1)	6 (2)	8 (3)	7 (2)	8 (5)
Newly defined CSA	1 (<1)	0	1 (<1)	0	0
Previously defined CSA	0	0	0	0	0
WBC	N=528	N= 248	N=254	N=419	N=147
Abnormal	23(4)	11(4)	12(5)	12(3)	10(7)
Newly defined CSA	14 (3)	3(1)	6(4)	6(1)	1(<1)
Previously defined CSA	1 (<1)	0	1(<1)	2(<1)	0
Hematocrit	N=265	N=257	N=262	N=147	N=147
Abnormal	18(7)	4(2)	14(5)	9(6)	11(8)
Eosinophils	N=530	N=253	N=262	N=418	N=147
Abnormal	10(2)	13(5)	6(2)	14(3)	15(10)
Basophils	N=531	N=251	N=262	N=419	N=147
Abnormal	19(4)	2(<1)	3(1)	19(4)	2(1)
AST, n (%)	N=545	N=256	N=258	N=423	N=147
Abnormal	20 (4)	6 (2)	10 (4)	59 (14)	22 (15)
Newly defined CSA	3(<1)	0	3(1)	11(3)	4(3)
Previously defined CSA	0	1(<1)	1(<1)	4(<1)	1(<1)
ALT, n (%)	N=540	N=252	N=262	N=423	N=147
Abnormal	23 (4)	7 (3)	10 (4)	79 (19)	30 (20)
Newly defined CSA	2(<1)	1(<1)	1(<1)	10(3)	8(5)
Previously defined CSA	2(<1)	1(<1)	1(<1)	10(2)	3(2)
Bilirubin, total, n (%)	N=257	N=245	N=254	N=147	N=147
Abnormal	6(2)	8(3)	4(2)	1(<1)	3(2)
Newly defined CSA	0	0	0	0	0
Previously defined CSA	0	0	0	0	0
GGT	N=429	N=149	N=156	N=423	N=147
Abnormal	22(5)	9(6)	2(1)	56 (13)	15 (10)
Newly defined CSA	5(1)	2(1)	0	16(4)	2(1)
Previously defined CSA	1(<1)	1	0	3(<1)	0
Creatinine,n (%)	N=544	N=253	N=260	N=424	N=147

Abnormal	7(1)	9(4)	7(3)	20(5)	17(12)
Newly defined CSA	0	0	1(<1)	1(<1)	1(<1)
Previously defined CSA	0	0	0	0	0
Urea, n(%)	N=534	N=249	N=259	N=421	N=147
Abnormal	48 (9)	13 (5)	19 (7)	51 (12)	29 (20)
Newly defined CSA	19(4)	3(1)	8(3)	34(8)	14(10)
Previously defined CSA	7(1)	0	1(<1)	9(2)	0
Sodium	N=542	N=252	N=261	N=423	N=147
Abnormal	32(6)	5(2)	16(6)	26(6)	8(5)
Newly defined CSA	5(1)	1(<1)	0	7(2)	0
Previously defined CSA	1(<1)	1(<1)	0	5(1)	0
Potassium	N=545	N=254	N=262	N=423	N=147
Abnormal	22(4)	2(<1)	9(3)	26(6)	9(6)
Newly defined CSA	7(1)	1(<1)	4(<2)	7(1)	3(2)
Previously defined CSA	5(<1)	1(<1)	2(<1)	5(1)	2(1)
Chloride	N=541	N=252	N=261	N=423	N=147
Abnormal	43(8)	6(2)	11(4)	29(7)	9(6)
Newly defined CSA	36(7)	2(<1)	3(1)	22(5)	4(3)
Previously defined CSA	1(<1)	0	0	0	0
Bicarbonate	N=418	N=149	N=156	N=421	N=147
Abnormal	27(6)	8(5)	10(6)	29(7)	15(10)
Newly defined CSA	8(2)	5(3)	8(5)	4(1)	7(5)
Previously defined CSA	9(2)	5(3)	8(5)	6(1)	7(5)
Blood in urine	N=519	N=252	N=255	N=418	N=147
Abnormal	45(9)	14(6)	13(5)	30(7)	8(5)
Hematocrit	N=265	N=257	N=262	N=147	N=147
Abnormal	18(7)	4(2)	14(5)	9(6)	11(8)
Eosinophils	N=530	N=253	N=262	N=418	N=147
Abnormal	10(2)	13(5)	6(2)	14(3)	15(10)
Basophils	N=531	N=251	N=262	N=419	N=147
Abnormal	19(4)	2(<1)	3(1)	19(4)	2(1)

* Only patients who had the laboratory tests performed are included in the denominator for each test.
Data were obtained from Sponsor's Table 3.2 from ISS and Tables 3.2.1-3.2.2.from the Sponsor's response to the information request from Aug 23, submitted Sept 18, 2006 as well as from Table 1.4 (ISS, response to IR from August 23, submitted on October 11, 2006). Revised Table 3.2.1 and 3.2.2 were submitted by the Sponsor in Response to IR, October 11, 2006, but not included in this Table due to several data discrepancies identified within the revised tables. Both original and revised Tables 3.2.1 and 3.2.2 show similar trends in the laboratory parameters.

Of the CBC parameters measured, slightly more patients from the PENNSAID® group showed changes from normal to newly defined clinically significantly abnormal in WBC compared to placebo (3% vs 1%), though the overall proportion of patients changing from normal to

abnormal in WBC was the same in the PENNSAID® and the placebo treated arms. There was no difference for change in hemoglobin, but a slightly higher proportion of patients developed decreases in hematocrit comparing to placebo. Slightly more patients in the PENNSAID® group developed changes in basophils, although this change was of uncertain clinical significance.

A higher proportion of patients from the oral diclofenac arm had a decrease in hemoglobin as compared to the PENNSAID® arm. However, the highest proportion of patients with changes in CBC parameters was observed in the combination arm (PENNSAID® plus oral diclofenac).

In regards to liver function, more patients in the PENNSAID® arm had elevations in LFTs compared to placebo, but the proportion of patients developing abnormal LFTs was still higher in the oral diclofenac arm compared with the PENNSAID® arm. The combination of oral and topical diclofenac resulted in even more patients developing changes from normal to abnormal than in the oral diclofenac alone group.

Examining renal function, a change in creatinine occurred in approximately equal proportions of PENNSAID®- and placebo-treated patients. Slightly more patients from the PENNSAID® group had changes in urea and bicarbonate compared to placebo. Treatment with oral diclofenac resulted in a higher proportion of patients changing from normal to abnormal and to CSA in that group comparing with PENNSAID® patients for all the measured renal parameters. The highest toxicity was again observed in the combination (PENNSAID® plus oral diclofenac) arm.

Small percentages of patients treated with PENNSAID® developed abnormalities in sodium and potassium comparing to placebo. Those changes were comparable to or slightly less than what was observed in the oral diclofenac arms. Of note, more patients treated with PENNSAID® changed from normal to abnormal for chloride (8%) which was higher than in the oral diclofenac arm (7%) or the combination (6%) arm. Further review of the mean changes in chloride (Table 43) showed that a slight increase in chloride occurred in PENNSAID® treated patients at week 4, but became negligible and equal to placebo at week 12. The significance of this change is unclear from the available data. Monitoring of chloride in addition to other parameters typically monitored with NSAIDs may be needed in clinical practice.

Data on laboratory changes from normal to abnormal and to CSA (newly and previously defined) from PEN-03-112 (not shown) were consistent with the pooled data shown.

Change over time in the laboratory parameters was assessed in study PEN-03-112E. The changes in the key laboratory parameters after 6 and 12 months of treatment with PENNSAID® are shown in Table 47.

Comparison of the proportion of patients, who changed from normal to abnormal after 6 and 12 months of treatment with PENNSAID® (Table 47), shows that additional cases of patients with abnormalities in liver enzymes, BUN, and creatinine accrued with longer exposure to PENNSAID®. No pattern of clinical adverse outcomes relating to the liver or kidneys was observed based on the reported AEs (section 7.1.5).

Table 47. Changes in laboratory parameters occurring over time in study PEN-03-112E

Parameter	Analysis Set		
	6 months	1 year	All patients
	N=460	N=143	N=780
Hemoglobin	24 (5.2)	13 (9.1)	39 (5.0)
	N=459	N=143	N=779
AST	28 (6.1)	13 (9.1)	50 (6.4)
ALT	32 (7.0)	11 (7.7)	57 (7.3)
GGT	30 (6.5)	15 (10.5)	52 (6.7)
Creatinine	21 (4.6)	14 (9.8)	47 (6.0)
Urea	44 (9.6)	26 (18.2)	86 (11.0)

Data from Sponsor's Table 30, study PEN-03-112E, p 68.

In conclusion, the toxicity profile of PENNSAID® (topical diclofenac sodium) obtained from the submitted laboratory data was overall similar to the toxicity profile of the approved oral formulation of diclofenac sodium (Voltaren XR) regarding the effects on hemoglobin, renal, and liver functions.

Less toxicity was observed after 3 months of PENNSAID® treatment compared to 3 months of oral diclofenac treatment, but abnormalities for all key parameters (hemoglobin, AST, ALT, GGT, creatinine, and urea) continued to accrue over time.

Patients treated with the combination of PENNSAID and oral diclofenac (Voltaren® XR) demonstrated the highest incidence of laboratory abnormalities, suggesting augmentation in renal, hepatic and hematological toxicity with the use of the combination of topical PENNSAID® and oral non-steroidal anti-inflammatory medications.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressure, heart rate, respiratory rate) were obtained at the baseline and final assessments in the following controlled studies: 102-93-1, 108-97, RA-CP-109, RA-CP-109US, PEN-03-110, PEN-03-112, and the extended 12 month open label study PEN-03-112E. Interim assessments were performed in the study PEN-03-112 at weeks 4 and 8 and in the study PEN-03-112E at weeks 14, 26, and 40.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Analyses for drug-control comparisons of vital signs were performed by the Sponsor on the data from study PEN-03-112. Additional analyses of blood pressure changes on the data pooled from

the six controlled trials and on the data from study PEN-03-112E were performed at the Division's request.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

In study PEN-03-112, comparison between the study arms demonstrated no difference in change in systolic or diastolic blood pressure, pulse rate or respiratory rate between the study arms (data not shown).

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

To assess individual patient changes, the proportion of patients with an increase in mean BP≥5mmHg was calculated in study PEN-03-112. Similar proportions of patients with the defined increase in mean BP were observed in the PENNSAID® and placebo groups. However, slightly higher percentages of patients were seen in the groups containing oral diclofenac:

- PENNSAID® plus oral placebo – 35 out of 153 patients (23%),
- topical placebo plus oral placebo- 36 out 157 patients (23%),
- oral diclofenac plus topical placebo-38 out 150 patients (25%),
- vehicle control plus oral placebo-30 out of 160 patients (19%),
- PENNSAID® plus oral diclofenac- 40 out of 150 patients (27%).

To assess the change in BP over time, study PEN-03-112E was analyzed to determine the proportion of patients who developed a ≥5mmHg increase in mean blood pressure. 189 out of 732 subjects who had both baseline and final BP assessments (26%) developed this predefined increase in BP, suggesting little change in the occurrence of HTN over time.

The degree in BP change was assessed in the controlled trials and compared between the five combined arms (PENNSAID®, placebo, oral diclofenac, vehicle control, and combination of PENNSAID® plus oral diclofenac) based on the proportion of patients with a 20% increase in diastolic BP from baseline to the final study visit. Table 48 shows that with PENNSAID® treatment slightly more patients developed increased BP according to this criterion as compared to placebo treatment. More patients from the oral diclofenac arms developed such change in BP.

Table 48. Proportions of patients with 20% increase in diastolic BP from baseline to the final study visit

Criterion of BP increase	PENNSAID® plus Oral diclofenac N=150	PENNSAID® N=826	Vehicle control N=520	Placebo N=248	Oral Diclofenac N=461
Patients with a 20% in diastolic BP, n (%)	9(6)	35(4)	21(4)	8(3)	33(7)

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The proportions of patients who had HTN of >150/100 at final study visit were compared between the five combined arms in the controlled phase III trials. Table 49 shows that a few cases of such increase in BP were noted in the PENNSAID®, vehicle control and placebo arms. The highest number of patients with such elevation in BP was observed in the oral diclofenac arm.

Table 49. Proportions of patients with BP >150/100 at final study visit.

Criterion for BP increase	PENNSAID® plus Oral diclofenac N=150	PENNSAID® N=826	Vehicle control N=520	Placebo N=248	Oral Diclofenac N=461
Patients with 150/100 at final study visit, n (%)	0	2 (0.2)	1(0.2)	1(0.4)	6 (1.3)

In study PEN-03-112E, 4 out of 751 (0.5%) patients who had baseline and final study assessments had BP >150/100 at any time during the study.

7.1.8.4 Additional analyses and explorations

Additional analyses of blood pressure changes were performed in study PEN-03-112E to determine the proportion of patients who developed the adverse event of "hypertension". The Sponsor applied the following criteria for adjudication of 'hypertension':
- elevated systolic BP (>20 mm Hg increase from baseline and absolute value ≥ 140 mm Hg (Whelton et al., 2002) and/or
- elevated diastolic BP (10 mm Hg increase from a baseline measurement of ≥95 mm Hg, or a 20 mm Hg increase to a final value >95 mm Hg from a baseline measurement of ≤ 95 mm).

There were 28 cases of HTN reported by the investigators as an adverse event of HTN in study PEN-03-112E. Since some of the patients had previous readings of elevated BP or established diagnoses of hypertension prior to study participation, the Sponsor requested re-adjudication of the cases by an independent expert (Dr. William B. White), blinded to study participation. Ten of these 28 cases were re-adjudicated as true adverse events of hypertension. According to the Sponsor, the calculated total patient-exposure to PENNSAID® was 436.8 patient years in this study. The resulted incidence of adjudicated HTN (10 cases) in this study was 2.3% per 100 person years, which appeared comparable to the estimated incidences of 3.4, 3.7, and 5.4 per 100 person years for celecoxib, oral diclofenac, and ibuprofen, respectively[11].

This reviewer reviewed the narratives for these 28 cases and disagreed with the previous re-adjudication in four cases (all of these four cases had been previously re-adjudicated as not representing adverse events of hypertension). Thus, the incidence of HTN calculated taking into consideration the 14 cases of hypertension with the total patient-exposure to PENNSAID® of 436.8 patient years resulted in the incidence of 3.2% per 100 person years. This incidence remains comparable with the incidences reported for oral NSAIDs as above, and reflects similar,

not lessened, risks for development of HTN with PENNSAID® treatment as compared with oral NSAIDs.

7.1.9 Electrocardiograms (ECGs)

The approved oral formulation of diclofenac sodium (VoltareXR®) has not been associated with ECG changes. Pulse rate data obtained during PENNSAID®'s development program did not reveal any safety signal in association with PENNSAID®. In view of the absence of a safety signal in the safety database it is not necessary to have clinical trial data on ECG changes prior to approval. However, this reviewer recommends the Sponsor make a postmarketing commitment to conduct a phase IV study investigating ECG changes in patients exposed to PENNSAID®.

7.1.11 Human Carcinogenicity

No increased risk for development of new malignancies or any particular type of malignancy was apparent with PENNSAID® treatment. One death in study 102-93-1 of unknown type of cancer after 22 days of treatment with study medication appears unlikely to be related to PENNSAID®. Three cases of newly diagnosed malignancies (bladder, breast, and stomach) among 795 enrolled patients were reported in the uncontrolled open-label study PEN-03-112E, which is not inconsistent with the expected malignancy rate in this patient population.

7.1.12 Special Safety Studies

For this program, special safety studies include dermatological skin irritation and sensitization studies 100-89, 101-89-2, 103-93-2, 104-93-3 and were reviewed in Dr. Hon-Sum Ko's Dermatology consultation report (May 16, 2002).

Study PEN-03-112E was a long term safety study of 12 month duration to assess the safety of PENNSAID® prescribed for up to 12 months, including long term dermatological and other potential safety concerns common to the pharmacological class of NSAIDs (cardiovascular, gastro-intestinal, renal, and hematological side effects). Because of the previous concerns based on prior animal studies about the potential for DMSO to cause ophthalmologic toxicity, particularly lens opacities and cataracts, ophthalmologic evaluations at baseline and final study visits were incorporated in this study. Seven hundred ninety-five patients were enrolled in the study (including 43 patients who were extended from study PEN-03-112). The study was powered to achieve the objective of treating at least 100 patients for 12 months and at least 300 patients for 6 months. After achieving this goal, the Sponsor discontinued the study. For this reason, 279 of the randomized 795 patients did not complete the study due to the study termination by the Sponsor.

For discussion of occurrence of AEs and laboratory abnormalities in this study refer to sections 7.1.3, 7.1.5, and 7.1.7.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No studies have been conducted to evaluate possible withdrawal effects of PENNSAID®. In general, no withdrawal effects are known in association with oral NSAIDs except flare of the underlying arthritis and/or pain. No formal follow up of study participants was done by the Sponsor after the final study assessment in both pivotal studies and the long term study PEN-03-112E. Below is the Sponsor's statement regarding the patient follow up in the PENNSAID® development program on p. 83 of the ISS:

"While no efficacy or specific safety measurements were made following completion of therapy in any clinical trial, patients were asked to report any adverse event that occurred for up to 4 weeks following the last dose of study medication. As the majority of patients in these studies were recruited from the investigator's own practice, there was opportunity for reasonable post-study surveillance for delayed adverse events including withdrawal effects. No such adverse events were noted."

Consequently, it is impossible to estimate the flare rate in patients with knee OA treated in the phase III controlled trials.

There was no evidence of abuse potential with PENNSAID® in any of the OA clinical trials reviewed.

7.1.14 Human Reproduction and Pregnancy Data

Diclofenac sodium administered orally (Voltaren ®) belongs to pregnancy category C. DMSO is not known to have any teratogenic effects on the human fetus, however, no studies have been done to address this. It is reasonable to believe that the teratogenic potential of PENNSAID® is similar to that of oral diclofenac sodium. However, due to the lack of definitive data about DMSO in this regard, PENNSAID® must not be used in pregnant women and nursing mothers.

7.1.15 Assessment of Effect on Growth

Since the proposed indication for use of PENNSAID® is osteoarthritis of the knee, a disease that occurs in the adult population, no studies with PENNSAID® have been done in pediatric population. Therefore no assessment of this drug's effect on growth have been made.

7.1.16 Overdose Experience

Doses of PENNSAID® solution administered in the development program varied from 5 drops four times/day (study 108-97) to 40 drops four times /day to 50 drops three times /day (study PEN-03-110). Refer to section 7.2 for a detailed description of study drug exposure. There was no apparent toxicity apart from the AEs rates and effects on the laboratory parameters described in Section 7.1. There were no incidences of overdosing of PENNSAID® reported in the OA studies. A theoretical possibility of drug overdose exists in the case when PENNSAID®, while

prescribed for knee OA, is used for application to other superficial joints. This was not reported in OA trials, and the outcome of such use is unknown.

7.1.17 Postmarketing Experience

PENNSAID® was approved in the United Kingdom in November 2000 and in Canada in March 2003. It has also been used in Italy and Portugal. The Sponsor submitted a summary of the worldwide experience on the safety of PENNSAID® for the period April 2003 to March 2006. These safety reports represent spontaneous reports submitted directly to the Sponsor and/or Regulatory Health Agency. The majority of these reports were received from the Canadian market. Overall, the same AE profile has been seen in the postmarketing as was observed in the controlled phase III trials.

Table 50. Adverse events reported in postmarketing in Canada and United Kingdom

Body System	Number of Events
Body as a whole	**35**
Abdominal pain	1
Asthenia	1
Back pain	2
Body odor	1
Chest pain	2
Edema	4
Face edema	1
Halitosis	5
Headache	6
Lack of Efficacy	2
Neck rigidity	1
Pain	9
Cardiovascular	**2**
Palpitation	2
Digestive	**12**
Diarrhea	1
Dyspepsia	2
Mouth ulceration	1
Nausea	6
Rectal hemorrhage	1
Ulcerative stomatitis	1
Metabolic and nutritional	**1**
Creatinine increased	1
Musculoskeletal	**2**
Leg cramps	1
Myalgia	1
Nervous	**14**
Dizziness	7
Drowsiness	1
Paresthesia	2
Paresthesia, app. site	4
Respiratory	**5**
Asthma	1
Dyspnea	2
Laryngismus	1
Pharyngitis	1
Skin and appendages	**29**
Contact dermatitis, app. site	6
Contact dermatitis with vesicles, app. site	2
Dry skin, application site	6
Eczema	1
Pruritus, app. Site	1
Rash	7
Skin discoloration	4

Urticaria	2
Special senses	17
Abnormal vision	1
Blurred vision	1
Cataract	1
Ear pain	1
Eye disorder	2
Eye pain	8
Taste perversion	3
Sponsor's Table 36, p 52, ISS. Reporting period: May, 2003 – March 31, 2006	

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The clinical development program and the included studies are outlined in Section 4.2, Table 4.

A total of 6425 patients were exposed to PENNSAID® in the 17 clinical trials. Table 51 shows all patients exposed to PENNSAID® in different trials, their duration and dose range used in those trials. A total of 44 patients were exposed to PENNSAID® in clinical pharmacology studies. A total of 300 patients were exposed to PENNSAID® in phase I controlled clinical trials. A total of 911 patients were exposed to PENNSAID® in phase III controlled clinical trials. A total of 5213 patients were exposed to PENNSAID® in uncontrolled clinical trials. Two thousand five hundred twelve patients were treated in the seven controlled phase III trials. One hundred fifty two patients were treated with the combination of oral diclofenac and PENNSAID®.

Table 51. Patient exposure to the study drug in PENNSAID®'s development program

Study Number	Where Conducted	Calendar Dates	Dose Range	Duration (days)	Number Exposed
102-93-1	Canada	Mar 23, 1994 – Feb. 1997	40 drops qid	42	(12)[1]
106-95	USA	Dec 3, 1995 – Apr 20, 1995	1 mL	1	6
RA-CP-109-US	USA	Dec. 19, 2000 – May 18, 2001	40 drops qid	84	(23)[1]
2663	Canada	Jan. 14, 2003 – Jan. 25, 2003	80 drops	1	18
2656	Canada	Jan. 13, 2003 – Feb. 5, 2003	80 drops qid	8	20
100-89	USA	May 5, 1994 – Jun 21, 1994	0.2 mL	48	25
101-89-2	USA	Feb 26, 1996 – Apr 16, 1996	0.2 mL	51	223
103-93-2	USA	Mar 28, 1996 – Mar 29, 1996	0.2 mL	1	25
104-93-3	USA	Mar 25, 1996 – May 10, 1996	0.2 mL	47	27
102-93-1	Canada	Mar 23, 1994 – Feb. 1997	Up to 80 drops qid	42	41
107-96	Canada	Jan 7, 1997 – July 18, 1997	Up to 80	28	84

			drops qid		
108-97	Canada	Sept. 1998 – April 1999	Up to 2 mL	42	50
RA-CP-109	Canada	Nov. 29, 1999 – Aug. 21, 2000	Up to 80 drops qid	42	107
RA-CP-109-US	USA	Dec. 19, 2000 – May 18, 2001	Up to 80 drops qid	84	164
RA-CP-110	Canada	Sept. 11, 2001 – Sept. 24, 2002	Up to 100 drops tid	84	311
PEN-03-112[2]	Canada, USA	Feb. 17, 2004 – Oct. 19, 2005	40 drops qid	84	154
EDR	Canada	Jul 14, 1994 – Apr 13, 1995	Up to 80 drops qid	0–9 months	207 (37)[3]
105-95	Canada	Mar 9, 1995 – June 27, 2000	Up to 80 drops qid	0–12+ months	4213
PEN-03-112E	Canada, USA	Mar. 3, 2004 – Nov. 1, 2005	Up to 80 drops qid	0–52 weeks	793

Data obtained from Sponsor's Table 2, p 14, ISS
[1]Patients are counted under the main Phase III study.
[2]An additional 152 patients received PENNSAID® plus oral diclofenac in this study
[3]Number in parenthesis refers to the number of patients exposed to PENNSAID® in the EDR program that participated in and are counted under Study 105-95.

7.2.1.1 Study type and design/patient enumeration

Table 4 (section 4.2) shows study design and Table 51 shows the PENNSAID® dose and patient enumeration in each study in the clinical program.

7.2.1.2 Demographics

The demographic characteristics of patients exposed to PENNSAID® in phase I and Phase III clinical trials are shown in Table 52 and Table 53. The distribution of gender and ethnicity was more balanced in the phase I skin safety controlled trials which mainly enrolled non-diseased volunteers. The majority of patients participating in phase III trials were Caucasians and females, reflecting the target population afflicted by primary osteoarthritis. Under-representation of other ethnicities is apparent and may make it difficult to generalize the exposure data to the more broad OA population (Table 52). The limitations of the data are described in the foot note: no data were available on race in the uncontrolled trials EDR and 105-95, 80 patients in the 105-95 study did not have gender records.

Table 53 shows that the majority of patients exposed to PENNSAID® were 51-80 years old with mean body weight of 185 lbs.

Table 52. Patients' characteristics in PENNSAID®'s development program (gender, ethnicity)

Study	No. Patients Exposed	Gender (M/F)	Ethnicity				
			Caucasian	Black	Hispanic	Asian	Other
[redacted]							
106-95	6	5/1	4	1	0	0	1
2663	18	9/9	14	3	0	1	0
2656	20	10/10	15	2	0	3	0
Total, N (%)	44	24/20 (55/45)	33 (75)	6 (14)	0 (0)	4 (9)	1 (2)
[redacted]							
100-89	25	13/12	16	0	9	0	0
101-89-2	223	119/104	91	68	53	5	6
103-93-2	25	13/12	14	0	9	1	1
104-93-3	27	16/11	24	0	3	0	0
Total, N (%)	300	161/139 (54/46)	145 (48)	68 (23)	74 (25)	6 (2)	7 (2)
[redacted]							
102-93-1	41	8/33	39	1	0	0	1
107-96	84	32/52	79	1	0	4	0
108-97	50	3/47	48	1	0	1	0
RA-CP-109	107	51/56	88	8	0	3	8
RA-CP-109-US	164	51/113	142	18	3	1	0
RA-CP-110	311	133/178	299	2	0	4	6
PEN-03-112	154	50/104	120	11	6	15	2
Total, N (%)	911	328/583 (36/64)	815 (89)	42 (5)	9 (1)	28 (3)	17 (2)
[redacted]							
EDR	207	86/121	N/A	N/A	N/A	N/A	N/A
EDR/105-95	37	11/26	N/A	N/A	N/A	N/A	N/A
105-95	4176	1472/2624[2]	N/A	N/A	N/A	N/A	N/A
PEN-03-112E	793	335/458	694	21	6	52	20
Total, N (%)	5213	1904/3229[2] (37/62)	N/A	N/A	N/A	N/A	N/A

[1] Data on race in uncontrolled studies only available for Study 112E
[2] Sex of 80 patients was not recorded in Study 105-95.

Data from Sponsor's Table 9, p 22, ISS

Table 53. Patients' characteristics in PENNSAID®'s development program (age, weight)

Study	No. Patients Exposed	Mean Age (years)	Number of Patients in Specified Age Range (years)									Mean Body Weight (lbs)
			<20	20 to 30	31 to 40	41 to 50	51 to 60	61 to 70	71 to 80	>80	NR	
[redacted]												
106-95	6	48.7	0	0	2	2	1	0	1	0	0	183.3
2663	18	32.6	0	9	5	4	0	0	0	0	0	164.7
2656	20	33.0	1	6	8	5	0	0	0	0	0	153.1
Total	44		1	15	15	11	1	0	1	0	0	
[redacted]												
100-89	25	48.2	0	3	6	6	3	6	1	0	0	N/A
101-89-2	223	44.7	3	20	57	93	24	16	9	1	0	N/A
103-93-2	25	46.9	0	5	2	8	4	5	1	0	0	N/A
104-93-3	27	58.5	0	2	3	7	7	4	4	0	0	N/A
Total	300		3	30	68	114	38	31	15	1	0	N/A
[redacted]												
102-93-1	41	60.1	0	0	1	9	11	12	7	1	0	180.2
107-96	84	62.5	0	1	2	11	21	21	27	1	0	178.9
108-97	50	64.7	0	0	0	3	12	21	14	0	0	152.7
RA-CP-109	107	65.0	0	0	1	9	30	27	33	7	0	197.8
RA-CP-109-US	164	63.4	0	0	0	22	46	49	40	7	0	204.4
RA-CP-110	311	64.3	0	0	0	34	81	97	84	15	0	194.4
PEN-03-112	154	61.7	0	0	1	20	52	47	31	3	0	190.7
Total	911		0	1	5	108	253	274	236	34	0	
[redacted]												
EDR	207	58.6	1	3	13	49	43	51	35	11	1	N/A
EDR/105-95	37	56.7	0	1	4	8	8	9	5	2	0	N/A
105-95	4176	56.1	50	131	378	702	762	734	581	107	731	N/A
PEN-03-112E	793	62.5	0	0	5	95	247	246	178	22	0	193.1
Total	5213		51	135	400	854	1060	1040	799	142	732	

Data obtained from Sponsor' Table 10, ISS, p 23

7.2.1.3 Extent of exposure (dose/duration)

The numbers of patients exposed to PENNSAID® for the specified durations in clinical pharmacology and Phase I controlled clinical trials are shown in Table 54. As shown, 287 patients were exposed to PENNSAID® for >30 days in these studies.

Table 54. Patient exposure to PENNSAID® in clinical pharmacology and phase I studies

Study	No. Patients Exposed	Number of Patients Exposed for Specified Durations			
		≤ 1 day	2–7 days	8–30 days	>30 days
[redacted]					
102-93-1	121	0	0	0	12
106-95	6	6	0	0	0
RA-CP-109-US	23[1]	0	0	1	22
2663	18	18	0	0	0
2656	20	0	1	19	0
Total, N (%)	79	24 (30.4)	1 (1.3)	20 (25.3)	34 (43.0)
[redacted]					
100-89	25	0	2	1	22
101-89-2	223	8	5	6	204
103-93-2	25	25	0	0	0
104-93-3	27	0	0	0	27
Total, N (%)	300	33 (11.0)	7 (2.3)	7 (2.3)	253 (84.3)

[1]Number in parenthesis refers to the number of patients exposed to PENNSAID® in this pharmacokinetic sub-study, that are counted in the overall summary under the main study listed in controlled clinical studies (Phase III).
Data obtained from Sponsor's Table 5, p19, ISS

Table 55 shows the number of patients exposed to PENNSAID for the specified durations in Phase III controlled clinical trials. In the controlled studies, 302 patients were treated with PENNSAID® for at least 85 days.

Table 55. Patient exposure to PENNSAID® in phase III trials

Study#**	Total No patients exposed with available data	Total No patients exposed	Number of patients exposed to PENNSAID for specific durations								
			0-14 days	15-28 days	29-42 days	43-56 days	57-70 days	71-84 days	85-90 days	>90 days	Unknown
102-93-1	41	41	5	1	33	2	0	0	0	0	0
107-96	84	84	7	71	6	0	0	0	0	0	0
108-97	50	50	6	8	33	3	0	0	0	0	0
RA-CP-109	106	107	7	8	74	17	0	0	0	0	1
RA-CP-109-US	160	164	9	11	8	7	4	42	76	3	4
RA-CP-110	305	311	26	27	19	19	12	57	140	5	6
PEN-03-112	151	154	7	12	8	4	8	34	78	0	3
Total	897	911	67	138	181	52	24	133	294	8	14
Cumulative*	897	911	897	830	692	511	459	435	302	8	14

*shows number of patients exposed to the study drug for the indicated period or longer
** Duration of exposure data were available for 106 of 107 patients from RA-CP-109, 160 of 164 for RA-CP-109-US, 305 of 311 for RA-CP-110, and 151 of 154 for PEN-03-112
Data obtained from Table 7 from Sponsor's ISS

As shown in Table 56, 170 patients were exposed to 45.5% DMSO for at least 85 days. Of the 152 patients treated with the combination of PENNSAID® and oral diclofenac, 76 were treated for at least 85 days.

Table 56 Patient exposure to treatments other than PENNSAID® in seven controlled trials in PENNSAID®'s development program.

Study Number[1]	Total No. Patients Exposed	Number of Patients Exposed for Specified Durations								
		0–14 days	15–28 days	29–42 days	43–56 days	57–70 days	71–84 days	85–90 days	>90 days	Unknown
[redacted]										
102-93-1	42	6	5	27	3	0	0	0	0	0
107-96	80	11	61	8	0	0	0	0	0	0
108-97	49	5	2	40	2	0	0	0	0	0
RA-CP-109	109	12	19	60	17	0	0	0	0	1
RA-CP-109-US	162	24	11	10	7	1	30	78	1	0
PEN-03-112	161	12	10	12	3	4	24	91	0	5
Total	**603**	**70**	**108**	**157**	**32**	**5**	**54**	**169**	**1**	**6**
[redacted]										
102-93-1	39	5	1	31	2	0	0	0	0	0
107-96	84	10	68	6	0	0	0	0	0	0
108-97	52	12	2	37	1	0	0	0	0	0
PEN-03-112	157	8	13	10	2	9	25	80	0	10
Total	**332**	**35**	**84**	**84**	**5**	**9**	**25**	**80**	**0**	**10**
[redacted]										
108-97	52	6	3	40	3	0	0	0	0	0
Total	**52**	**6**	**3**	**40**	**3**	**0**	**0**	**0**	**0**	**0**
[redacted]										
RA-CP-110	311	30	24	14	17	4	51	155	9	7
PEN-03-112	151	9	8	6	7	3	26	90	0	2
Total	**462**	**39**	**32**	**20**	**24**	**7**	**77**	**245**	**9**	**9**
[redacted]										
PEN-03-112	152	12	8	9	10	2	32	76	0	3
Total	**152**	**12**	**8**	**9**	**10**	**2**	**32**	**76**	**0**	**3**

[1] Duration of exposure data was available for only:
Pennsaid: 106 of 107 patients in RA-CP-109
160 of 164 patients in RA-CP-109-US
305 of 311 patients in RA-CP-110
151 of 154 in PEN-03-112
Vehicle Control: 108 of 109 patients in Study RA-CP-109
156 of 161 patients in Study PEN-03-112
Placebo: 147 of 157 patients in Study PEN-03-112
Oral Diclofenac: 304 of 311 patients in Study RA-CP-110
149 of 151 patients in Study PEN-03-112
PENNSAID + Oral Diclofenac: 149 of 152 patients in Study PEN-03-112
Data obtained from Sponsor's Table 4, ISS and Table 2.2-ISS from Response to Info request submission on Sept 18, 2006

Since patients in study PEN-03-112 were allowed to treat one knee (study knee) only, and patients in study RA-CP-109 were required to treat the study knee and allowed to treat the contra-lateral knee as needed, the daily mean dose was different in the two studies. In study PEN-03-112, the mean daily dose of study solution containing PENNSAID® was 5.1gm/day and the mean daily dose of study solution with vehicle control was 5.2 gm (Table 57). In study RA-CP-109US, the mean dose of study solution was 8.8 gm/day for the patients exposed to PENNSAID® and 8.7 g/day for the patients exposed to 45.5% DMSO vehicle control (Table 58).

Table 57. Daily average and total dose of PENNSAID® in study PEN-03-112

Variable		Group 1 PEN+OD N=152	2 PEN+OP N=154	3 VC+OP N=161	4 P+OP N=157	5 P+OD N=151
Total dose (g)	N	121	127	121	123	119
	Mean (SD)	361.8 (191.2)	391.7 (196.2)	351.6 (198.0)	349.2 (195.1)	366.9 (179.9)
	Median	410.6	418.7	370.0	368.0	395.1
	Range	4.9–708.6	9.3–698.3	2.8–699.5	0.0–720.1	6.1–714.5
Daily average dose (g)	N	121	126	119	119	119
	Mean (SD)	5.1 (1.7)	5.34 (1.79)	5.20 (1.82)	5.08 (1.65)	5.05 (1.82)
	Median	5.2	5.34	5.20	5.05	4.92
	Range	0.82–9.34	1.03–12.25	1.06–10.79	0.52–8.67	0.42–11.04
Daily exposure by dose range, N(%)	≤ 4.2 g/d	30 (19.7)	31 (20.1)	36 (22.4)	30 (19.1)	41 (27.2)
	>4.2, <5.2g/d	29 (19.1)	29 (18.8)	24 (14.9)	38 (24.2)	24 (15.9)
	>5.2, ≤ 6.2g/d	31 (20.4)	25 (16.2)	25 (15.5)	22 (14.0)	25 (16.6)
	>6.2 g/d	31 (20.4)	41 (26.6)	34 (21.1)	29 (18.5)	29 (19.2)
	Unknown	31 (20.4)	28 (18.2)	42 (26.1)	38 (24.2)	32 (21.2)

Data obtained from Sponsor's Table 28, PEN-03-112 study report

Table 58. Daily average and total dose of PENNSAID® in study RA-CP-109US

Study arm	Dose applied per day (grams)					Number of patients with a dose of			
	Mean	SD	Min	Max	N	≤ 5 g/day	>5 & ≤10 g/day	>10 & ≤15 g/day	>15 g/day
PENNSAID®	8.8	3.3	2.2	17.4	160	17	93	45	5
45.5% DMSO	8.7	3.1	0.1	16.2	162	19	89	49	5

Data obtained from Sponsor's Table #73, p 187, RA-CP-109US study report

Forty-three patients receiving PENNSAID® and oral placebo in the study PEN-03-112 were extended to study PEN-03-112E. In the uncontrolled study PEN-03-112E, 463 patients completed 6 months of treatment and 144 completed at least 12 months of treatment. The median exposure to PENNSAID® for these 144 patients was 376 days. Patient exposure to PENNSAID® in the uncontrolled studies is shown in Table 59.

Table 59. Patient exposure to PENNSAID® in uncontrolled studies

Study Number	No. Patients Exposed	Number of Patients Exposed for Specified Durations[1]					
		0–4 weeks	5–12 weeks	13–26 weeks	27–52 weeks	>52 weeks	Unknown
EDR	207	193	10	4	0	0	0
EDR/105-952	37	5	1	2	6	23	0
105-95	4176	2030	491	315	514	826	0
PEN-03-112E	793	53	102	143	332	116	47
Total, N (%)	5213	2281 (43.8)	604 (11.6)	464 (8.9)	852 (16.3)	965 (18.5)	47 (0.9)

[1]Duration periods shown are for study PEN-03-112E; corresponding duration periods for EDR and 105-95 are: 0–1 month, 1–3 months, 3–6 months, 6–12 months and 12+ months
[2]Some patients who participated in the EDR program also participated in Study 105-95. The duration of exposure for these patients was determined from the start of the EDR program to the end of Study 105-95.

Data were obtained from Sponsor's Table 8, p 20, ISS

The daily and cumulative dose of PENNSAID® in study PEN-03-112E is shown in Table 60. Patients participating in that study were also allowed to treat the contra-lateral knee.

Table 60. Average daily and cumulative dose exposure in study PEN-03-112E

Variable		All patients N=793
Total dose1 (g)	Mean (SD)	1471 (1297)
	Median	1147
	Range	4–6757
Daily average dose (g)	Mean (SD)	7.81 (3.74)
	Median	7.30
	Range	0.4–25.2
Exposure by dose range, N (%)	≤5 g/d	131 (16.5)
	>5, ≤10 g/d	230 (29.0)
	>10, ≤15 g/d	130 (16.4)
	>15 g/d	21 (2.6)
	Unknown	281 (35.4)

[1]Dose includes treatment received under initial study PEN-03-112 for Group 2 (PENNSAID® + oral placebo) direct extension patients
Data obtained from Sponsor's Table 10, p 36, and Tables 14.3.8 and 14.3.4 from PEN-03-112E study report

7.2.3 Adequacy of Overall Clinical Experience

This application and review rely primarily on the seven phase III controlled clinical trials and one uncontrolled open label trial PEN-03-112E for evidence of safety of PENNSAID®. These seven controlled trials provide placebo-, vehicle-, and oral diclofenac- controlled experience with PENNSAID® in 2513 patients with osteoarthritis and provide a sufficiently large primary database for this disease. In the studies PEN-03-112 and the extended study PEN-03-112E, 463 patients completed 6 months of treatment with PENNSAID® and 144 patients completed 12 months of treatment with PENNSAID®. This number of patients is adequate and slightly exceeds the minimum size of the safety database recommended in the ICH EI document for products intended for long term treatment of non-life threatening conditions. The assessment of long term safety in this review is based on a median duration of 376 days of exposure to PENNSAID® in 144 patients who completed 12 months of treatment in study PEN-03112E, which is adequate to make a safety assessment for the purposes of approval.

7.2.5 Adequacy of Routine Clinical Testing

The methods and timing of acquisition of vital signs, laboratory, and AE data were overall adequate. The laboratory data were not collected in studies 108-97, RA-CP-109 and RA-CP-109-US, and this was indicated in the NDA 20-947 Not Approval letter dated 8/07/02. However, the adequate design and timing of safety data acquisition in studies PEN-03-112 and PEN-03-112E, conducted with guidance from the Division, provide a sufficient basis for assessment of safety of PENNSAID® .

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and drug interaction appears adequate and is discussed in Dr. David Lee's Clinical Pharmacology review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

PENNSAID® is a topical solution containing 1.5% diclofenac sodium, and is anticipated to have an AE profile similar to that of oral diclofenac. These AEs were adequately addressed by the Sponsor (section 7.1). The route of administration of PENNSAID® predisposes to the appearance of application site reactions. The Sponsor adequately assessed application site reactions in the development program (sections 7.1.5 and 7.1.12).

45.5% DMSO is included in the formulation as a dermal penetration enhancing component. Some of the animal studies demonstrated a remote potential for DMSO to cause ophthalmologic

toxicity. The Sponsor incorporated ocular evaluations in the design of studies PEN-03-112 and PEN-03-112E and assessed the potential for PENNSAID® to cause ophthalmologic AEs (section 7.1.3.1).

This reviewer recommends further study of PENNSAID® regarding the following safety issues:
- Collecting and analyzing data on cases of retinal detachment and cataract appearance and progression in patients treated with PENNSAID® in spontaneous postmarketing reports.
- Conducting a pregnancy registry for women who become pregnant while exposed to PENNSAID® to identify the pregnancy outcome and postnatal health status of children.

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review are of acceptable quality and include seven phase III clinical trials in OA that were multi-center, randomized, double-blind, placebo- and vehicle-controlled. The data from the five arm trial PEN-03-112 and the long term safety trial PEN-03-112E are of high quality and were referred to throughout the safety assessment of the data pooled from the seven controlled phase III trials. Overall, the results of the safety evaluation were consistent between the reviewed pools. The studies enrolled a representative patient population with knee OA and addressed the safety of the combination therapy of topical PENNSAID® with oral NSAIDs, exemplified by addition of oral diclofenac sodium (Voltaren® XR) to PENNSAID® in study PEN-03-112.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Important AEs likely to be treatment related are application site dermatological reactions, and all the reactions common to the class of NSAIDs including increased risk of cardiovascular events, as well as gastro-intestinal, renal, hepatic and hematologic effects (section 7.1).

7.3.1 Application site reactions

Incidence of application site reactions including dry skin, contact dermatitis, contact dermatitis with vesicles, paresthesia, vasodilation, acne, pruritis and urticaria was higher in patients who received PENNSAID®, compared to placebo (52% vs 16%). Although the majority of the skin reactions were skin dryness, about 9% of patients treated with PENNSAID® in controlled trials and 13% of patients treated with PENNSAID® in the uncontrolled trial PEN-03-112E developed contact dermatitis compared to 2% of patients receiving placebo. Contact dermatitis with vesicles was seen in 2% of patients treated with PENNSAID® in controlled trials and in 10% of patients treated with PENNSAID® in the uncontrolled, open label trial PEN-03-112E.

7.3.2 Other AEs common to the class of NSAIDs

AEs related to gastro-intestinal symptoms, such as dyspepsia, abdominal pain, flatulence, diarrhea, nausea, and constipation occurred in a higher proportion of patients treated with

PENNSAID® compared to placebo, but the observed rate of each of these AEs was lower in the PENNSAID® treated patients than in patients treated with oral diclofenac or the combination of oral and topical diclofenac. The proportion of patients with GI hemorrhages in PENNSAID® treated patients appeared similar to that of patients treated with oral diclofenac, but the incidence of melena was lower in the PENNSAID® group as compared to the oral diclofenac group. Risk of rectal hemorrhages was increased with the combination treatment (PENNSAID® and oral diclofenac).

The risk of cardiovascular events was not clearly less with PENNSAID® treatment comparing to oral diclofenac treatment. Cardiovascular events appeared to occur at equal rates in patients treated with PENNSAID® and oral diclofenac. However, the small number of events in each group precluded drawing more definitive conclusions. The incidence of HTN was similar with PENNSAID® treatment when compared to other oral NSAIDs (section 7.1.8).

The frequency of occurrence of edema and peripheral edema as well as increase in creatinine and urea was higher in PENNSAID® group comparing to placebo but lower comparing to oral diclofenac group after 3 months of treatment. After prolonged (6-12 months) treatment with PENNSAID®, the proportions of patients developing abnormalities in creatinine and urea appeared to increase.

In the PENNSAID® group, more patients developed elevations in liver function tests compared to placebo. However, less liver toxicity was observed in the PENNSAID® group than with oral diclofenac alone or in combination with PENNSAID®.

Patients treated with PENNSAID® had more pronounced decrease in hemoglobin compared to patients treated with placebo, but less then patients treated with oral diclofenac. After 12 months of treatment with PENNSAID®, the proportion of patients with change in hemoglobin from normal to abnormal increased.

Toxicity of the oral diclofenac was augmented by the addition of PENNSAID® for all parameters described above.

Overall, it appears that the lessened adverse effects on the GI tract, kidneys, liver, and hematological parameters achieved by PENNSAID® are balanced by the increased rate of the application site reactions related to the proposed topical application of PENNSAID®.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

This safety review pooled data across the seven phase III clinical trials as discussed above and one uncontrolled study of long term safety of PENNSAID® monotherapy.

7.4.1.1 Pooled data vs. individual study data

Comparison between the pooled data and the individual studies data (PEN-03-112 and PEN-03-112E were made throughout the review (section 7.1).

7.4.1.2 Combining data

This review combines studies by simple combination of numerators and denominators and does not employ other pooling procedures.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose ranging studies were not conducted with PENNSAID®, so it is not possible to explore for dose dependency of adverse events. Of note, the results of pharmacokinetic studies (refer to Dr. David Lee's Clinical Pharmacology review) have shown that the systemic levels of diclofenac sodium achieved after a single dose topical application of PENNSAID® to two knees (40 drops to each) were 187-200 times lower than after a single oral dose of 50mg tablet of Voltaren ® XR, suggesting that systemic exposure to diclofenac with PENNSAID® is low.

7.4.2.2 Explorations for time dependency for adverse findings

To assess if the most common AEs associated with PENNSAID® increased in frequency over time, the data from study PEN-03-112E were examined and are shown in Table 61. No increase in appearance of AEs was observed over time, except HTN that seemed to slightly increase over time (see section 7.1.8 for discussion of HTN).

Table 61. AEs occurring over time in ≥ 5% patients in study PEN-03-112E

Adverse Events versus Onset of the Event (Number and % of Patients)

Body system	Preferred term	Onset of the Event				
		0–13 weeks N=746	14–26 weeks N=580	27–39 weeks N=448	40–52 weeks N=230	53–65 weeks N=116
Body as a whole	Accidental injury	19 (2.5)	8 (1.4)	8 (1.8)	5 (2.2)	0 (0.0)
	Back pain	17 (2.3)	7 (1.2)	5 (1.1)	1 (0.4)	0 (0.0)
	Headache	21 (2.8)	6 (1.0)	3 (0.7)	3 (1.3)	0 (0.0)
	Pain	9 (1.2)	4 (0.7)	4 (0.9)	2 (0.9)	0 (0.0)
Cardiovascular	Hypertension	9 (1.2)	8 (1.4)	6 (1.3)	5 (2.2)	0 (0.0)
Digestive	Liver function tests abnormal	4 (0.5)	18 (3.1)	11 (2.5)	3 (1.3)	1 (0.9)
Musculoskeletal	Arthralgia	30 (4.0)	12 (2.1)	12 (2.7)	6 (2.6)	0 (0.0)
Respiratory	Bronchitis	9 (1.2)	10 (1.7)	9 (2.0)	0 (0.0)	0 (0.0)
	Respiratory disorder	19 (2.5)	14 (2.4)	15 (3.3)	1 (0.4)	2 (1.7)
Skin and appendages	Contact dermatitis, application site	43 (5.8)	44 (7.6)	21 (4.7)	8 (3.5)	1 (0.9)
	Contact dermatitis with vesicles, application site	29 (3.9)	34 (5.9)	5 (1.1)	7 (3.0)	0 (0.0)
	Dry skin, application site	117 (15.7)	51 (8.8)	20 (4.5)	12 (5.2)	3 (2.6)

Source: Sponsor's Table #14 from PEN-03-112 study report

The table includes only the events with known onset date for patients with known duration of treatment. The events are displayed in 3 months intervals. Incidence is calculated by taking the number of events divided by the number of patients treated for at least the minimum number of days for that interval.

Refer to section 7.1.7 for additional discussion of time dependency of the adverse reactions.

7.4.2.3 Explorations for drug-demographic interactions

To examine the incidence of AEs in relation to age, drug-demographic interactions were explored in study PEN-03-112. No particular differences in drug-demographic interactions were observed in PENNSAID®- and placebo- treated patients. In the long term safety study PEN-03-112E, patients ≥ 65 years old developed more abnormalities in renal function and had more application site reactions when compared to patients younger than 65 years old (Table 62).

Table 62. AEs in relation to age in study PEN-03-112E

Event	Age <65 y/o N=459	Age ≥ 65 N=334
Hypertension	14 (3%)	14 (4%)
Creatinine increased	6 (1%)	13 (4%)
Dry skin, application site	110 (24%)	91(27%)
Contact dermatitis, application site	45 (10%)	58 (17%)
Contact dermatitis with vesicles, application site	39 (8%)	36(11%)

Data obtained from Source Table 14.3.28, study PEN-03-112E

7.4.2.5. Explorations for drug-drug interactions

Refer to section 7.1 for discussion of efficacy and safety of the combination arm (the topical and oral diclofenac sodium). Refer to section 8.2 for discussion of the anticipated PENNSAID®'s interactions with other drugs. No formal exploratory analysis was performed on the submitted data.

7.4.3 Causality Determination

AEs that were most clearly associated with PENNSAID® administration were application site reactions. Other adverse effects that were associated with PENNSAID® administration were those in the spectrum of the known AE profile of the approved oral formulation of diclofenac sodium (Voltaren® XR).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose for administration of PENNSAID® (40 drops 4 times /day) was chosen empirically. According to the Sponsor, the initial dose of 1.5% diclofenac sodium in PENNSAID® was based on the composition of similar products available in Europe when PENNSAID®'s development began in the late 1980s, particularly based on the dosing regimen of Voltaren Emulgel - 1.16% (diclofenac diethylammonium), that was also prescribed 4 times a day. This information guided the formulation and the recommended dose of the final patented product PENNSAID®. This dose appeared to be safe when used in an open, unblinded fashion for over 10 years under extemporaneous compounding provisions.

The mechanism of the clinical effect of PENNSAID® is unclear, but is presumed due to anti-inflammatory and analgesic effects of locally elevated levels of diclofenac in the underlying joint and surrounding tissues following topical administration of PENNSAID®. Results of pharmacokinetic studies (refer to Dr. David Lee's Clinical Pharmacology review) have shown that the systemic levels of diclofenac achieved after a single dose topical application of PENNSAID® to two knees (40 drops to each) were 187-200 times lower than after a single oral dose of 50 mg tablet of Voltaren®XR. Thus, the traditional approach of blood-level response to varied doses of product may not explain this product's clinical effect or guide the appropriate dose selection.

One potential possibility to explore the effect of PENNSAID® would be measuring the levels of diclofenac sodium in the synovial fluid from the knee joint after application of PENNSAID®. This was attempted in study #102-93-1 in two healthy volunteers. It was concluded from that study that after 42 hours of PENNSAID® administration, the synovial fluid concentration level of diclofenac sodium from the two patients taken 6.9 hours and 13 hours after the last application of PENNSAID® were less than 10 ng/ml. Similar levels of diclofenac (<10ng/ml – under the limit of quantification) were observed in plasma of nine healthy volunteers in the same study.

No other attempts to determine the mechanism of action of topical diclofenac were undertaken by the Sponsor. Two literature reports exploring the mechanism of action of diclofenac gel (1.16% Voltaren Emulgel) revealed controversial findings (discussed in detail in Dr. Averbuch's review of the study #102-93-1). Therefore, it remains unclear, whether the transdermal delivery of diclofenac sodium aids the direct penetration of the active ingredient to the diseased joint or if the levels initially rise in the systemic circulation, later resulting in appearance of diclofenac sodium in the synovial fluid. A possible effect of PENNSAID® not only on the joint structures but also on the surrounding soft tissues can not be excluded and likely also takes place.

The proposed empiric dose and regimen appear to provide adequate safety. There are no dose modifications from the proposed dose.

8.2 Drug-Drug Interactions

The anticipated drug interactions for PENNSAID® lie in the spectrum of those of the approved oral formulation of diclofenac sodium (Voltaren® XR). No formal studies of the potential for drug interaction with PENNSAID® were conducted by the Sponsor.

According to the Sponsor (p 70, ISS):
*"There were no adverse event reports of possible drug interaction between concomitant medications (*used by patients enrolled in the PENNSAID®'s development program*) and the study drug. In patients using warfarin, there were no adverse events of uncontrolled international normalization ratio (INR) or requirement for unexpected adjustment of warfarin dose".*

8.3 Special Populations

Efficacy and safety of PENNSAID® has not been studied in pediatric population, or pregnant and/or lactating women. PENNSAID® must not be used in these special patient populations. Patients older than 65 years of age developed more application site reactions comparing with patients younger than 65 years (see section 7.4.2.3).

8.7 Postmarketing Risk Management Plan

The clinical development plan for PENNSAID® did not identify safety risks that would warrant a formal risk management plan. Therefore, none was submitted. Refer to section 9.3 for recommendations for postmarketing risk management plan and required post marketing commitments.

8.8 Other Relevant Materials

Review of this application included consultations from the Division of Anti-Infective and Ophthalmology Drug Products (DAIODP), the Office of Surveillance and Epidemiology, the Division of Surveillance, Research and Communication Support (OSE, RMP), the Division of Drug Marketing, Advertising, and Communications (DDMAC), and the Division of Safety Inspections (DSI). Additionally, a consultation from the Division of Dermatologic and Dental Drug Products (DDDDP) was obtained during the previous review cycle (May 16, 2002).

9 OVERALL ASSESSMENT

9.1 Conclusions

1. PENNSAID® is modestly effective (see Section 6) for the treatment of patients with mild to moderate osteoarthritis of the knee. This assessment is based on the modest effect size substantiated across 4 studies (two adequate and well controlled and two supportive phase III clinical studies). PENNSAID® was associated with improvement in signs and symptoms of osteoarthritis of the knee measured by WOMAC pain, physical function, and stiffness dimensions, and improvement in patient global and overall health assessments. The two pivotal studies were adequately large, multi-center, randomized, placebo- and vehicle- controlled and provided statistically persuasive evidence of benefit of PENNSAID® over placebo. The consistency of PENNSAID®'s effect across multiple endpoints and multiple subgroups combined with statistically significant results provides convincing evidence of modest efficacy.

2. The safety profile of PENNSAID® appears acceptable for the treatment of mild to moderate osteoarthritis of the knee. The safety profile of PENNSAID® is similar to that of the approved oral formulation of diclofenac sodium (Voltaren XR®) with the addition of application site reactions, related to PENNSAID®'s route of administration. While

some of the systemic effects associated with administration of oral diclofenac sodium are lessened with administration of topical PENNSAID®, appearance of the application site reactions adds additional burden to the safety considerations while assessing the risk-benefit ratio.

3. Application site reactions and AEs in common with other NSAIDs will limit the tolerability of PENNSAID®.

4. The use of PENNSAID® in combination with oral NSAIDs should not be recommended due to an increased incidence of adverse events including rectal hemorrhages and augmentation of hepatic, renal, and hematological toxicity associated with use of oral NSAID alone.

5. The safety and efficacy of PENNSAID® has not been established in patients with renal and hepatic insufficiency and in women who are pregnant or nursing.

9.2 Recommendation on Regulatory Action

This clinical reviewer recommends approval of PENNSAID® for improving signs and symptoms of knee osteoarthritis in patients with mild to moderate osteoarthritis of the knee.

It is clear that substantial numbers of patients with OA of the knee will not be able to tolerate PENNSAID® because of the application site reactions and the adverse drug reactions it shares with other NSAIDs. Nonetheless, given the high prevalence of knee OA and its impact on public health and the diversity of patient characteristics and co-morbidities, it is the opinion of this reviewer that PENNSAID® (topical diclofenac sodium) should be included in the armamentarium of treatment options for patients with osteoarthritis of the knee.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management actions are recommended. A consult from OSE was obtained and indicated that they did not anticipate that a topical formulation would have additional safety concerns for which a Risk Minimization Action Plan (Risk MAP) or RMP to minimize risk would be normally expected. It was also noted in the consultation that oral diclofenac does not have any risk management tools beyond standard product labeling and the NSAID Class Medication Guide.

9.3.2 Required Phase 4 Commitments

There are no required phase IV commitments.

9.3.3 Other Phase 4 Requests

The Sponsor should conduct a phase IV study investigating ECG changes (including QTc interval changes) in patients receiving PENNSAID®. A study of ECG changes is not required prior to approval because diclofenac is approved for systemic use and because review of the safety database did not reveal a safety signal of arrhythmias to suggest QT prolongation.

This reviewer recommends the Sponsor also agree to:

3. Collecting and analyzing post-marketing spontaneous reports on the incidence rate of retinal detachment and cataract appearance and progression in patients treated with PENNSAID®.
4. Conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to PENNSAID® to identify the pregnancy outcome and postnatal health status of children.

9.5 Comments to Applicant

None.

10 APPENDICES

Appendix A.
Descriptions of Serious Adverse Events associated with PENNSAID® occurred in phase III controlled clinical trials studies

Study #	Treatment at event	Patient #	Sex	Age	Serious AE preferred term	Duration of exposure	Outcome	Important co-morbidities
102-93-1	PENNSAID	232*	M	43	Right leg and foot pain	3 days	recovered	Allergy to adhesive tape
107-96	PENNSAID	1032*	F	74	CVA, manifested by aphasia and confusion	16 days	unknown	HTN, previous CVA
107-96	PENNSAID	4023	M	66	Elective ablation of accessory myocardial pathway	12 days	recovered	Cardiac arrhythmia
108-97	PENNSAID	06-118**	F	73	Myocardial infarction	Angina- day 9 MI- day 14	Recovered from MI, angina continued	Hypercholesterolemia
108-97	PENNSAID	09-012**	F	76	Newly diagnosed lung cancer	42 days	unknown	unknown
RA-CP-109	PENNSAID	B01-013**	F	79	Fell off stepladder, fractured right foot	18 days	Treated with casting	unknown
RA-CP-109-US	PENNSAID	28-011**	F	68	Angina, anxiety attack	1 day	Recovered	unknown
RA-CP-109-US	PENNSAID	39-002	M	54	Angina	9 days	Cardiac bypass surgery, recovered	CAD, previous MI
RA-CP-110	PENNSAID	34-001(?*)	M	68	CVA, critical carotid artery stenosis	74 days	Carotid endarterectomy, recovered surgery	Previous CVA, HTN
PEN-03-112	PENNSAID + oral diclofenac	13-011*	M	56	Right leg cellulitis (study knee)	48 days	Treated with a/b, recovered	Prior surgical repair of the right quadriceps tendon
PEN-03-112	PENNSAID + oral diclofenac	21-008*	F	61	Unstable angina	75 days	Quadruple cardiac bypass surgery, recovered, CAD recurred in May 2005	Hypercholesterolemia, DM-II, previous h/o angina, HTN
PEN-03-112	PENNSAID + oral diclofenac	23-001	F	52	TIA/CVA	35 days	recovered	HTN, DM, hyperlipidemia, mild carotid atherosclerosis, mild aortic stenosis

* the study drug was discontinued after SAE occurrence
** unknown if the study drug was discontinued after the SAE occurrence

Appendix B.
Serious adverse events in study PEN-03-112.

PEN-03-112	PENNSAID + oral diclofenac	13-011*	M	56	Right leg cellulitis (study knee)	43	Treated with a/b, recovered	Prior surgical repair of the right quadriceps tendon
PEN-03-112	PENNSAID + oral diclofenac	21-008*	F	61	Unstable angina	75	Quadruple cardiac bypass surgery, recovered, CAD recurred in May 2005	Hypercholesterolemia, DM-II, previous h/o angina, HTN
PEN-03-112	PENNSAID + oral diclofenac	23-001	F	52	TIA/CVA	35	recovered	HTN, DM, hyperlipidemia, mild carotid atherosclerosis, mild aortic stenosis
PEN-03-112	Vehicle-control /oral placebo	05-007	M	76	Acute enteritis	63	Treated with a/b, recovered	None
PEN-03-112	Placebo solution +oral placebo	07030	F	84	Left leg swelling/anemia	12	Unknown/transfusion, recovered	Previous h/o PE, on oral anticoagulation
PEN-03-112	Placebo solution +oral placebo	14006	F	73	Left hip fracture	17	Underwent surgical repair, recovered	None
PEN-03-112	Placebo solution +oral placebo	66016	M	83	CVA	50	Unknown	HTN
PEN-03-112	Placebo solution +oral placebo	76015	M	68	Prosthetic hip dislocation	34	Surgical repair, recovered	HTN, s/p right total hip replacement
PEN-03-112	Placebo solution + oral diclofenac	37003	F	74	Lower GI bleeding post polypectomy	25	Recovered after blood transfusion	H/o colon polyps

Appendix C
Serious adverse events, other than death (uncontrolled trials 105-95 and PEN-03-112E)

Study #	Treatment at event	Patient#	Sex	Age	Serious AE preferred term	Duration of exposure at event	Outcome	Important co-morbidities
105-95	PENNSAID	887*	F	55	Crohn's ileitis	60 (2mo)	Right hemicolectomy, recovered	Unclear prior h/o Crohn's disease
PEN-03-112E	PENNSAID	03018**	M	77	Acute anterolateral MI	(4 ½ mo)	recovered	CAD, HTN, S/p MI x 2, CHF
PEN-03-112E	PENNSAID	03019**	M	57	Acute inferior MI	26	PTCA, recovered	HTN, hypercholesterolemia, DM
PEN-03-112E	PENNSAID	12203	M	75	Acute MI	36	recovered	CAD, s/p CABG x 2
PEN-03-112E	PENNSAID	53011**	M	56	Acute MI	(2 ½ mo)	recovered	No prior h/o CAD or HTN
PEN-03-112E	PENNSAID	12214	F	67	Right CAD occlusion with collateral flow formation presenting with angina and tachyarrhythmia	(8 mo)	Permanent pacemaker placement	TIA, hypercholesterolemia
PEN-03-112E	PENNSAID (prior 5 week treatment with oral diclofenac in PEN-03-112)	21002	F	78	Angina	12+ mo	Recovered, angina relieved by 1 spray of Nitroglycerine	H/o angina, HTN, obesity
PEN-03-112E	PENNSAID (prior 3 mo treatment with oral diclofenac in PEN-03-112)	24020**	M	57	Angina, Left main coronary artery occlusion	14 weeks (3 ½ months)	Emergency bypass surgery, recovered	DM, HTN, hypercholesterolemia
PEN-03-112E	PENNSAID	25002**	65	M	Angina	10 mo	Recovered	H/o angina, hypercholesterolemia
PEN-03-112E	PENNSAID	25227**	M	57	Angina with classic radiation	5	Recovered, antihypertensive medication added	Hypercholesterolemia, poorly controlled HTN, narcolepsy
PEN-03-112E	PENNSAID (prior 3 mo	27006	F	63	Angina, atrial fibrillation	13 mo (including 3 mo in PEN-03-112)	recovered	HTN, h/o angina, DM-II, patient stopped beta-blocker

	treatment with PENNSAID+OP in studyPEN-03-112)							therapy 5 days prior to the event
PEN-03-112E	PENNSAID	45009	M	76	TIA	8 weeks	recovered	Previous silent CVA, HTN, Hypercholesterolemia, DM
PEN-03-112E	PENNSAID	01204*	F	84	Lower GI bleed	3 mo	Recovered, but had several recurrent events	Diagnosed with MM and possible IBD (Crohn's)
PEN-03-112E	PENNSAID	35006*	M	70	Upper GI bleeding	9 mo	Treated endoscopically with epinephrine injection into prepyloric ulcer followed by H.pylori treatment regimen, recovered	Previous h/o gastric ulcer
PEN-03-112E	PENNSAID (prior 3 mo treatment with Vehicle control in study PEN-03-112)	36010*	M	77	Partial small bowel obstruction	10 days (discontinued 3 weeks prior to the SAE)	Hospitalization, conservative management, recovered	Previous h/o multiple abdominal operations, and episodes of abdominal obstruction
PEN-03-112E	PENNSAID	01205*	M	80	Pneumonia/COPD exacerbation	8 mo	Hospitalization, standard treatment	h/o COPD
PEN-03-112E	PENNSAID	03018**	M	77	Pneumonia	41/2 mo	Hospitalization, MI, treatment (refer to the same patient in the cardiovascular SAE), recovered	h/o CAD, HTN
PEN-03-112E	PENNSAID	27201**	M	77	Pneumonia	5 mo	Hospitalization, recovered	
PEN-03-112E	PENNSAID	03010*	F	74	COPD exacerbation	7 ½ mo	Hospitalization, recovered	Previous h/o COPD
PEN-03-112E	PENNSAID	27017*	F	61	COPD first time diagnosed	8 ½ mo	Hospitalization, standard treatment, inhalers given at	H/o smoking

							discharge	
PEN-03-112E	PENNSAID (prior 3 mo treatment with Vehicle Control in PEN-03-112)	27016*	F	63	Bilateral Pulmonary Embolism	8 ½ mo	Hospitalization, anticoagulation, recovered	
PEN-03-112E	PENNSAID (prior 3 mo treatment with Vehicle Control in PEN-03-112)	15001***	M	70	Achilles tendon rupture, post-surgical wound infection	2 mo	Appropriate treatment, recovered	
PEN-03-112E	PENNSAID	22002	F	68	Infected total hip prosthesis	2 ½ mo	Prolonged IV antibiotics, recovered	
PEN-03-112E	PENNSAID	25232*	M	67	Total knee replacement, post surgical infection	2 ½ mo	IV antibiotics, no further information available	
PEN-03-112E	PENNSAID	44225** (product continued to the left knee)	M	52	Arthroscopic Right knee synovectomy/ post-procedure infection while temporarily off PENNSAID treatment	5 mo	Recovered	
PEN-03-112E	PENNSAID	07005***	F	72	Bladder cancer diagnosed by cystoscopy	3 ½ mo	unknown	h/o of microscopic hematuria at baseline study assessment, prior to use of study medication
PEN-03-112E	PENNSAID (prior 3 mo treatment with PENNSAID and oral diclofenac in PEN-03-112)	32026***	F	57	Ductal Carcinoma in situ, left breast	2 mo	Lumpectomy	
PEN-03-112E	PENNSAID	44228*	M	66	Stomach cancer	3 mo	Chemotherapy	
PEN-03-112E	PENNSAID (prior 3 mo treatment with Vehicle Control	12008	F	72	Slipped and fractured left ankle	7 mo	Recovered	

	in PEN-03-112)							
PEN-03-112E	PENNSAID (prior 3 mo treatment with PENNSAID and oral diclofenac in PEN-03-112)	25014*	F	79	Had an accident and fractured hip	3 weeks	Surgical repair	
PEN-03-112E	PENNSAID	25238*	F	45	Accidental Fracture, Left elbow	2 mo	Surgical repair,	h/o osteoporosis
PEN-03-112E	PENNSAID	32025***	M	62	Fall, resulting in right quadriceps tendon tear	3 weeks	Surgical repair	
PEN-03-112E	PENNSAID	47008	M	53	Surgical repair of shoulder ligament tear	3 mo	Recovered	Shoulder ligament tear occurred before study enrollment
PEN-03-112E	PENNSAID	01205***	M	80	Urinary retention, UTI, enlarged prostate, atrial fibrillation	2 weeks	Hospitalization	H/o prostatic hypertrophy; h/o CAD, atrial fibrillation
PEN-03-112E	PENNSAID	03210	F	57	Acute delusional episode	6 mo	Hospitalization, recovered	h/o disassociative disorder and depression
PEN-03-112E	PENNSAID	07004**	M	65	Kidney stone first episode	2 mo	Transurethral cystoscopy and removal of solitary stone	
PEN-03-112E	PENNSAID	08036	F	69	Lip swelling, right wrist arthritis and hives	5 mo	Treated with IV ab, recovered with continuous elevation of serum creatinine	
PEN-03-112E	PENNSAID	09005	M	67	Transurethral resection of prostate	4 mo	No reported complications	h/o BPH
PEN-03-112E	PENNSAID (prior 3 mo treatment with PENNSAID and oral diclofenac in PEN-03-112)	12023***	F	45	Anxiety attack, right arm pain, syncope	9 mo	recovered	H/o anxiety disorder, permanent pacemaker
PEN-03-112E	PENNSAID (prior 3 mo	25002* (study	M	65	New onset painful superficial	10 ½	Treatment with chronic	

	treatment with topical and oral placebos in PEN-03-112)	medication was continued on the contra-lateral knee)			thrombophlebitis and varicose vein network of the inner aspect of the right knee		anticoagulation	
PEN-03-112E	PENNSAID	25231*	M	70	Retinal detachment (70%); left eye	1 mo	Left eye surgery, further status unknown	
PEN-03-112E	PENNSAID	25234***	M	57	Polyarthralgia	2 mo	Treated with steroids	
PEN-03-112E	PENNSAID	47016	F	82	Syncope secondary to hypotension and bradycardia	5 mo	Hospitalization, change in antihypertensive meds	H/o CAD, TIA, HTN

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Pennsaid
NDA 20-947

Medical Officer Review

Submission Date:	August 7, 2001
Received Date:	August 8, 2001
Review Date:	February 1, 2002
Drug Name:	PENNSAID®
Composition (%w/w):	diclofenac sodium (1.5), dimethyl sulfoxide (45.5), propylene glycol ——— glycerine ——————— ethyl alcohol ——— purified water ——— b(4)
Applicant:	Dimethaid International, Inc.
Related Reviews:	Statistics, Chemistry, Pharmacology, Biopharmaceutics, Dermatology (consult)
Pharmacologic category:	NSAID
Proposed Indication:	Relieve of signs/symptoms of knee osteoarthritis
Dosage forms and route:	Topical solution
Submission type:	Original NDA
Materials Reviewed:	Primary documents- volumes 1 and 35-43 (hard copy-stamped pages only) Word documents (no pagination) -Item 3 -B. Intended Use.doc -H. Clinical.doc -I. Integ_Ben_Risk.doc -Item 8 -B. Overview of clin_invest.doc -G. Integrated Sum Efficacy.doc -H. Integrated Sum Safety.doc -J. Integr_Been_rsk_2001.doc

Orig NDA # 20-947
HFD-550/Div File
HFD-550/PM/Gould
HFD-550/Pharm/
HFD-550/Chem/
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Witter/Simon

(James Witter, M.D., Ph.D. Medical Officer)

Pennsaid: NDA # ——— b(4)

Table of Contents

Pennsaid ———————

Listing of NDA Review Tables

b(4)

Pennsaid Executive Summary

- Pennsaid is a topical solution that contains 1.5% diclofenac sodium (an NSAID), 45% DMSO, ——propylene glycol, ——ethyl alcohol and purified water. b(4)
- Dimethaid, the Sponsor of Pennsaid, is seeking approval for treatment of the signs and symptoms of the osteoarthritic knee.
- To demonstrate efficacy in treatment of the osteoarthritic target knee, a topical agent must demonstrate superiority over a placebo/standard-of-care treatment in three co-primary endpoints of pain, function, and a patient global.
- If approved, Pennsaid would be the first anti-inflammatory/analgesic topical to be marketed in the United States. Pennsaid was approved in the United Kingdom but only 4 of 13 other potential European countries also allow its marketing.
- The patients in the pivotal efficacy trials were allowed to treat the non-target knee during the trial if it was symptomatic on a "compassionate basis". Such treatment was also intended to decrease the use of acetaminophen as a rescue throughout the trial.
- There appears to be underreporting of adverse events both during the IND studies and in post-marketing reports. Clinical laboratory data for the two pivotal studies in this NDA were not collected
- From the data in this NDA, it can not be concluded that topical treatment with Pennsaid (10 drops to all four surfaces of the knee, applied four times daily) to only the osteoarthritic target knee for 6 weeks (study 109) or 12 weeks (study 109-US) is more efficacious than treatment with the control DMSO solution. This group is referred to as the "1 knee only" group in this review.
- It can not be concluded from the data in this NDA that Pennsaid treatment to the target knee throughout the study, and to the non-target knee for part of the study, is efficacious at the target knee compared to the DMSO control. This group is referred to as "both knees" in this review.
- It can not be concluded from the data in this NDA that Pennsaid treatment to the target and non-target knee (referred to as "2-knees" in this NDA) for the entire study is efficacious than the DMSO control to the non-target knee. However, Pennsaid does appear to be more effective than DMSO at the target knee in this situation. It is unclear if this latter result reflects a "double-dose" of Pennsaid or one of its constituents.
- Pennsaid has not been shown to be effective for treatment of the osteoarthritic hand.
- DMSO (i.e. all the constituents of Pennsaid without diclofenac sodium) treatment appears to be an active component of Pennsaid. This may explain the failure of Pennsaid demonstrate efficacy superior to DMSO.
- Use of Pennsaid does not seem to lessen the use of acetaminophen rescue.
- It can not be concluded from data in this NDA that Pennsaid treatment is safe, especially since the two pivotal trials were conducted without clinical laboratory assessments. Nonetheless, there are suggestions that Pennsaid is associated with changes in certain important clinical laboratory parameters in short-term studies.
- Therefore, there is insufficient information to conclude that topical Pennsaid solution should be approved for treatment of OA of the knee. Future studies should include an oral NSAID to allow for robust comparisons of safety and efficacy data.

Recommendations for Regulatory Action:

- This NDA should not be approved based on:
  - inadequate evidence of efficacy for the treatment of OA of the knee
  - inadequate evidence of safety
    - controlled clinical safety data will be necessary to assess the safety of Pennsaid as well as DMSO alone

BACKGROUND AND OVERVIEW:

Diclofenac, approved by the FDA as Voltaren® (NDA 19-201, approved July 28, 1988), Cataflam® (NDA 20-142, approved Nov. 24, 1993), Voltaren®-XR (NDA 20-254, approved March 8, 1996) and Arthrotec® (NDA 20-607, approved Dec. 24, 1997), is indicated for the treatment of the signs and symptoms of osteoarthritis (OA). Total daily oral doses of diclofenac range from 100-200 mg; dosing intervals range from once daily to TID depending on the drug. No topical formulation of diclofenac, or any other NSAID (non-steroidal anti-inflammatory drug) in a topical formulation, has received FDA approval for use in OA.

Studies to support the NDA approval of the oral diclofenacs noted above have mostly involved patients with OA of the hip or knee. According to the 1988 FDA Guidelines, drugs for OA needed to demonstrate improvement in pain and patient global. New draft guidance for OA (released 1999) recommends use of the WOMAC index for pain and function along with a patient global; all three endpoints are co-primaries and must independently achieve statistical significant over placebo. According to the current OA guidance, two trials of 12-week duration are considered necessary for new therapies while for traditional oral NSAIDs, replicate 6-week studies may be sufficient for approval. However, although not specifically addressed in the 1999 OA guidance, topical formulations of NSAIDs require 12-week studies since they represent a different route of drug administration. Lacking prior approvals for topically applied NSAIDs in OA (or for any valid pain model), **there is no precedent to base only 6-week exposures for these new routes (and potentially different mechanism of action) such as topical NSAIDs, as is the case with oral NSAIDs.**

PENNSAID® is produced by Dimethaid Corporation. It is a topical solution containing diclofenac sodium 1.5% w/w in **a 'patented' carrier solution containing 45.5% (w/w) dimethyl sulfoxide (45.5% DMSO), propylene glycol ——— glycerin ——— and ethanol ———** Dimethaid is seeking approval of Pennsaid for use in OA. Although DMSO (see below) is thought to facilitate skin penetration of diclofenac, blood levels of diclofenac with this topical formulation are (see PK review for details) in the range of 130-150 fold lower than blood levels reported following use of a single 50 mg of oral diclofenac. This estimate is based on a blood level of diclofenac sodium less than 10 ng/mL that was detected after a SINGLE application (1 mL) of Pennsaid (data from section entitled 'Related Drugs Containing Diclofenac Sodium', unpaginated Word document entitled Application summary which was part of the original NDA). In the trials noted below, **Pennsaid at 40 drops (which equals 1 mL in certain parts of the NDA and 1.4 mL in others) four times daily** was applied to one or more joints for lengths of time up to 12 weeks (see Table 21, Exposures with Pennsaid Use). However, it is problematic to make any safety assumptions from a single-dose experience with Pennsaid to patients receiving at least a range of 320 (single joint treated in 12 weeks) to 640 (two knee joints treated in 12 weeks) Pennsaid applications.

b(4)

This NDA review will focus on two of the five "pivotal" clinical trials, RA-CP-109 and RA-CP-109US, that were included as part of the NDA database for approval (see Table

1). The other three trials will be only summarized since they do not provide "adequate and well controlled" evidence to support the efficacy of Pennsaid for OA involving the knees (2 studies) or hands (1 study).

Diclofenac sodium belongs to a class of compounds colloquially referred to as NSAIDs. These compounds are thought to act in vivo primarily by inhibition of the cyclooxygenase (prostaglandin G/H synthase) an enzyme that facilitates (via other enzymes) the formation of prostaglandins from arachidonic acid. It is widely accepted that NSAIDS, through this inhibition, derive both their analgesic and anti-inflammatory properties. It is now recognized that there are two isoforms of cyclooxygenase, COX-1 and COX-2 and they serve different homeostatic and pathophysiologic functions in the body. It has been argued that this difference in function accounts for both the therapeutic as well as the adverse effects of NSAIDs. Diclofenac is considered to be a "non-selective" inhibitor of cyclooxygenase (i.e. it inhibits both COX-1 and COX-2), in contrast to more recent COX-2 selective agents.

Dimethyl sulfoxide, a critical and prominent component of Pennsaid, is a small molecule (m.w.78.13) that is one of the first compounds tested for permeation-enhancing properties. Several mechanisms of action of DMSO include:

- displacement of water from the stratum corneum lipid head groups and loosening of the dense polymeric structure of the protein molecules of the corneocytes
- extracts stratum corneum lipids, lipoproteins, and nucleoproteins, altering the barrier function and thereby increasing drug permeability
- enhances drug permeation by osmotically delaminating the stratum corneum, disrupting its structure, and thereby increasing drug permeability

It is unclear to what extent DMSO has in facilitating entry of diclofenac or the other ingredients in Pennsaid into the body, however, some studies suggest that only at concentration > 60% can DMSO enhance drug penetration of skin. **There is no information provided in the NDA regarding joint concentrations of diclofenac or any other constituent of Pennsaid to substantiate the theory that DMSO facilitates transport of compounds into the body.**

DMSO is a clear, colorless liquid that is miscible with water and most organic solvents. It is produced in large quantities as a byproduct of the paper pulp industry and is useful as a degreaser, solvent for synthetic fibers, pesticides, resins, dyes, pigments and as a paint stripper. A veterinary grade solution of DMSO is also available. Nonetheless, there are suggestions that DMSO has anti-inflammatory activity. In fact, DMSO is approved in Canada for the topical treatment of scleroderma (**Kemsol®**) and in Canada and the United States (1978, NDA 17-788) for bladder irrigation for interstitial cystitis (**RIMSO-50®**; 50% aqueous solution with 50 ml instill directly into the bladder for 15 minutes with repeats every 2 weeks as needed to maximum relief).

Drug Facts and Comparisons, Jan. 2000, p. 576-577 for Rimso-50 notes that **'unlabeled uses' for DMSO include '*scleroderma, arthritis, tendonitis, bursitis*'** along with other quite different uses such as herpes virus infections and stroke. **Mechanisms of action in the pharmacology section of** this information note that **DMSO** has '***anti-inflammatory action, membrane penetration, antifungal activity, cryproprotective effects for living cells and tissues, dissolution of collagen, nerve blockage, diuresis, cholinesterase inhibition, vasodilation and muscle relaxation'***. This same labeling notes that DMSO, because of its '*cutaneous transport characteristic, impurities and contaminants may be systemically absorbed from topical use'*.

The RIMSO-50 information also notes that **DMSO is not a benign medicine.** By virtue of its ability to liberate histamine, '*hypersensitivity (e.g. anaphylactoid symptoms) reactions may occur with topical administration*'. Other warnings or precautions for use include regular ophthalmic observations due to changes observed in the refractive index of the ocular lens and opacities in animals (monkeys, dogs and rats) given DMSO. It is **recommended that liver and renal function tests and complete blood counts be monitored while on therapy.** It is also noted that a '*severe peripheral neuropathy has also occurred when topical DMSO was used concurrently with sulindac*' which is an oral NSAID.

> ***Reviewer's comment:*** *A 63 year-old with arthritis treated for 6 months with sulindac initiated topical application of 90% DMSO and experienced a mixed sensorimotor peripheral neuropathy and segmental demyelination. Recovery was gradual, but incomplete (Reinstein, L; Arch. Phys. Med. Rehabil, 63, 581-84(1982). It is both unfortunate, and worrisome, that there are no other studies that address the potential systemic interactions of DMSO with NSAIDs and COX-2 agents since these are likely to be used together in patients with OA.*

Besides the potential for '*a garlic-like taste*' that '*may appear within minutes of administration*' there may also be a similar '*odor on the breath and skin may be present and remain for up to 72 hours.*' The following **adverse reactions to DMSO** also are listed in the *Drug Facts* information: '*sedation (52%), nausea (32%), headache (42%), dizziness (18%), burning or aching eyes (9%), vomiting (6%), local dermatitis (3.5%), erythema, itching, burning, discomfort, maceration, scaling, dermatitis, transient disturbances of color perception, photophobia, flu syndrome, diarrhea, weight loss and gain, sore throat, cough and anorexia.*'

The current formulation of Pennsaid, [redacted] was developed in Canada where it was available for compounding at the request of physicians. The sponsor estimates that by the early 1990's, over [redacted] such prescriptions had been compounded. **Pennsaid is currently marketed in the United Kingdom (approval November 21, 2000).** However, **no dose-ranging studies of Pennsaid have been conducted to date. In fact, no drug concentration information was sought in study RA-CP-109.**

b(4)

This NDA review will attempt to summarize the evidence provided by the Sponsor that Pennsaid, a topically applied NSAID, is efficacious and safe in the treatment of OA of the knee. One of the studies (108-97, see below) failed in a study involving OA of the hand. No studies have been conducted in this NDA to address OA of the hip (or other areas such as spine) due to perceived limitations (i.e. inability to penetrate to that level from the skin).

From an efficacy perspective, this NDA needs to establish that a topically administered NSAID is efficacious at each joint to which it is applied. This is because blood (10 patients, study 102-93-1, see PK review for details) and synovial fluid (2 patients, also from study 102-93-1) measurements of diclofenac even at steady state (i.e. after 42 days of four times daily treatment) are below the limit of detection (10 ng/mL) by GC/MS quantification. In essence, a local rather than a systemic effect needs to account for efficacy since blood concentrations are not sufficient to contribute any systemic (including the CNS) analgesic effects as with oral NSAIDs. On the other hand, it should be noted that the mechanism(s) of pain in a knee with OA are not well understood. For example, it is unclear what contribution bone and its periosteum, tendons and ligaments, muscle, joint capsule, menisci and synovium play in pain generation at various stages of OA. Ironically, **cartilage,** a key structural feature of joints, which is lost with progressive OA, is both **avascular and aneural. Therefore, if it is true that blood concentrations of NSAIDs are basically sub-therapeutic with Pennsaid, efficacy for symptom improvement must be rigorously established for each joint that is treated with a topical agent.** This requirement is not the case with oral NSAIDs since it has been established by clinical trials and experience with these agents that they can relieve pain in more than one joint in OA when given orally. Whether a distant joint, say the contralateral knee, is improved with a topical agent applied to the "target" ipsilateral knee is of interest (since it may have implications regarding a placebo effect, for example), but not as essential as establishing efficacy at the target knee. Efficacy must be established at every joint where a topical agent is applied.

Regulatory History/NDA Review Approach:

IND 42,773 was submitted on June 8, 1993. A **partial hold** letter was issued on **September 16, 1993 (CMC and toxicology)**; this hold was removed June 7, 1995. The **original NDA for Pennsaid was submitted December 15, 1997 but withdrawn on October 27, 1998.** The December 16, 1998 letter included 14 major/minor chemistry issues along with one medical deficiency i.e. study 102-93-1 did not provide substantial evidence of efficacy (no statistical difference). The current NDA was **resubmitted on August 7, 2001.**

Meetings with the Sponsor included teleconferences (Guidance-3/1/95, 6/6/95, 3/97, 1/14/98, 8/25/99, 9/27/00, 9/29/00: Special information/guidance- 10/23/00, 10/25/00) and a pre-NDA meeting (6/5/00). Multiple discussions focused on the assessment of efficacy for Pennsaid since topical anti-inflammatory and analgesic agent had (and have still) not been approved for OA. The efficacy issues mostly revolved around the fact that it

appeared that either the primary clinical outcome or the joint selected in the studies were not benefited by treatment with Pennsaid. For example, the failure of treating OA of the hand (study 108-97, see below) may have been the result of the AUSCAN index utilized in this study or that Pennsaid is not efficacious for OA of the hand. Similarly, failure to improve OA of the knee in study 102-93-1 may have been the result of using a non-validated study endpoint (i.e. the Daily Global Comparison, see below), or it may also have meant that Pennsaid is not efficacious for OA of the knee. The Sponsor was eventually encouraged to utilize the WOMAC index for knee (especially for pain and function assessment) since this was a highly validated clinical outcome index (via studies with oral NSAIDs and COX-2 agents) for OA of the knee.

Of note, one of the two pivotal efficacy trials **RA-CP-109** (the other being RA-CP-109-US) in this NDA **was never submitted to the IND (see June 5, 2000-FDA meeting minutes, page 3)**; rather it had been submitted to the Canadian regulatory authorities. Therefore, **the Division had no opportunity for input regarding trial design since the Sponsor did not request guidance.** At that same meeting, discussion between FDA and the Sponsor included whether study RA-CP-109 could be extended to a 12-week trial since the OA guidance required replicate 12-week studies for approval of new agents. Owing to the novel method of delivery of NSAID (i.e. topical), a similar requirement was stressed to the Sponsor for Pennsaid. To fulfill the requirement for two adequate and well-controlled trials for OA (of the knee), the Sponsor committed to another study (RA-CP-109-US) that would be a 12-week study conducted in the US.

> ***Reviewer's comment:*** *It is important to note that at no time in any FDA discussions was it noted by the Sponsor that patients in both 109 and 109-US may be receiving therapy to more than one knee in a trial. Nor was there ever any request for FDA to grant any sort of waiver from the requirement that the laboratory and clinical safety of Pennsaid must be established throughout its development, including phase 3 trials. Although study 109 was never extended to a 12-week trial as had been discussed, this study is still being considered as an adequate trial for this review since meeting minutes (October 25, 2000-FDA minutes, page 3) had suggested that this approach may be acceptable to the Division.*

Review of this NDA has presented special problems. Initial information that was submitted with the NDA included a paper copy of the protocols and their results along with electronic documents that were NOT electronic versions of the paper NDA, but rather summaries and discussions (i.e. various *Word* documents) of the results of the trials included in the NDA. Unfortunately, these electronic summaries where **not paginated** and data **tables in them were also mostly unnumbered, and the data contained in them often inconsistent,** when compared to data in other tables in other portions of these same documents. Therefore, due to the fact that tables and pages were unlabeled in these electronic documents, and that they were not cross-referenced to the original paper NDA, review this NDA was difficult and often confusing.

This difficulty was pointed out to the Sponsor during a teleconference (March 2002) after which the Sponsor submitted a major amendment to the NDA in the form of an electronic (PDF) version of the original paper NDA. However, this document did not match the paper NDA exactly and was also not paginated.

In response to information requests (March 19 & 28, 2002) intended to clarify how the trials 109 and 109-US had actually been executed and analyzed, the Sponsor submitted (April 3, 2002) individual patient line listings which described which knee had been the target knee for both treatment and efficacy throughout these trials. **In this reply it became clear that most of the patients (about two-thirds) in both study 109 and 109-US had their two knees treated during the entire study but only one had been assessed for efficacy.** However, such treatment as noted in these protocols was on a "compassionate basis" (as described later in this review); it was not based on a trial design basis (i.e. statistical plan specifying different treatment strata and their respective analyses). It was noted in these protocols that such use would allow less use of rescue medication throughout the trials, however, rescue medication was not an efficacy endpoint in these pivotal trials. **Importantly, these listings now serve in this NDA as the FDA medical officer and statistician's primary analysis tool to categorize patients with regard to actual treatment received by each patient in study 109 and 109-US and form the basis for efficacy assessment of these protocols.**

Therefore, in this NDA, there will be substantial differences between how the Sponsor and the FDA viewed the data and the conclusions reached by each. These differences will be noted at various locations in this NDA. This NDA review will transition from Sponsor-generated data and analyses to FDA-generated analyses of the data.

> ***Reviewer's comment:*** *An example of the difficulty in reviewing the data submitted in this NDA is given below in a table (footnotes are the reviewer's) for study 109-US (from April 3, 2002 submission, noted above).* ***Again,*** *information in the four attachments of this submission was not paginated and* ***the data,*** *as exampled in this summary table,* ***is both internally inaccurate*** *and even differs from the data that it is supposed to summarize as noted below.*

Pennsaid® Study RA-CP-109-US: Summary of Exposure Listing

Treatment[3]	*Pennsaid*	*DMSO*	*Total*
1 knee	*38*[2]	*33*	*70*[1]
2 knees	*101*[2]	*33*[1, 2]	*210*
Both knees	*23*[2]	*19*	*42*[2]
Total	*161*	*162*	*323*

1 *Examples of internally incorrect data: 70 ≠ 38 +31; 101+33 ≠ 210.*
2 *Examples of differences with MO review (see Tables later in this review) of same data: 38 = 37, 101 = 100, 33 = 110, 23 = 24, and 42 = 43.*
3 *Both knees refers to treatment that involved both knees to a variable degree during the trial*

NDA 20-947:

All studies included in Pennsaid NDA 20-947 are briefly summarized in **Table 1.**

Table 1: Listing of studies included in NDA 20-947[1]

Category	# Subjects/ Patients	Study	Short Description
ADME	8	106-95	single dose
ADME/PK	12	102-93-1	six week, QID dosing, synovial fluid/plasma analyzed
ADME/PK	23	109-US	PK portion of clinical trial, see below
Derm	25	100-89*	irritation/sensitization
Derm	223	101-89-2*	irritation/sensitization
Derm/OA	41	102-93-1	sensitization/OA-knee
Derm	25	103-93-2*	single dose, photoirritation
Derm	27	104-93-3*	sensitization
Derm/OA	84	107-96*	sensitization, OA-knee
———	50	108-97	42 days, 5-40 drops, QID
OA-knee	107	109	42 days, 40 drops, QID (pivotal efficacy)
OA-knee	164	109-US	84 days, 40 drops, QID (pivotal efficacy)
safety	2654	105-95	open label use (see safety review)
safety	244	EDR[2]	open label use (see safety review)

1. Number of patients refers to those exposed to Pennsaid in the trial. EDR = emergency drug release.

b(4)

Reviewer's comment: Studies 109 and 109-US (see below) will be reviewed in this NDA review. For those readers with more interest in these topics, studies marked (*) have been reviewed for dermatologic safety by Hon-Sum Ko, MD while the overall safety of Pennsaid is reviewed by Tatiana Oussova, MD. The PK review was by Dr. Bashaw.

Efficacy Assessment in NDA 20-947:

Studies in the NDA that discussed efficacy included five double-blinded, placebo-controlled trials conducted in OA patients experiencing pain in the knee ——— The **two "pivotal" efficacy studies (RA-CP-109 and RA-CP-109-US), both of a "flare" design, are the primary focus of the efficacy review in this NDA.** The other studies are summarized (see below) and will be discussed as may be necessary in the remainder of this review.

b(4)

The studies for efficacy submitted by the Sponsor in this NDA are summarized in the **Table 2.**

Table 2: Efficacy Studies for NDA 20-947

Protocol	Number of Patients (ITT) in Treatment Groups[1]					Study Duration (days)	Target[3]
	Pennsaid	**DMSO 45%**	**DMSO 4.5%**	**Placebo**	**Total**		
108-97	50	49	52	42	193	42	hand
102-93-1	41	42	39	-	122	42	knee
107-96	84	79	85	-	248	28	knee
RA-CP-109[2]	105	108	-	-	213	42	knee
RA-CP-109-US[2]	161	162	-	-	323	84	knee
Total[4]	441	440	176	42	1099	-	-

1. Pennsaid contains diclofenac 1.5% (w/w), DMSO 45.5%, propylene glycol and glycerine —— —— and ethyl alcohol ——— DMSO 45% is Pennsaid except diclofenac. DMSO 4.5% has increased concentrations of propylene and glycerine ——— to compensate for the lower concentration of DMSO. Placebo has neither DMSO or diclofenac; this is not the same placebo as described below for studies 102-93-1 and 107-96.
2. **As noted above, studies RA-CP-109 (from prior FDA-Sponsor meeting agreement) and 109-CP-109US were submitted as pivotal efficacy studies.**
3. For knee assessment, only one knee (identified in the CRFs) in each patient was studied as the target joint.
4. Numbers verified (see below) by MO review of line listings for studies 107-96, RA-CP-109 and RA-CP-109-US.

b(4)

Studies 108-97, 102-93-1 and 107-96, which are not considered as "pivotal" trials in this NDA review, are summarized below:

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Study 102-93-1:
This study was a randomized, placebo-controlled (**placebo H** = 'control' = DMSO 45%; **placebo L** = 'placebo' = DMSO 4.5%), three-arm parallel, **42-day** clinical trial to evaluate the safety and efficacy of Pennsaid for **OA of the knee.** The **primary endpoint was 'Daily Global Comparison'** which was a question that asked, 'Compared to yesterday, my treated knee feels: ___ the same, ___better, ___worse'. The investigator evaluated the application site weekly (with further testing) which comprised the sensitization portion of this trial (see Dr. Ko's review).

Once again, although (according to the Sponsor) patients with Pennsaid had a trend to more pain relief days as assessed by the primary outcome, **statistically significant differences were only observed against placebo L, not placebo H.** Also, one-way and two-way ANOVA at the 5% level revealed no significant differences among the treatment arms for any of the other variables studied.

> ***Reviewer's comment:*** *According to the July 19, 2002 request for information, the Sponsor stated that 56% of patients (i.e.68 of 122) had only the target knee treated for the entire study while the remaining 44% had both target and non-target knees treated throughout the trial. This suggests that the DMSO component of Pennsaid has efficacy.*

Study 107-96:
This was a double-blinded, randomized, **28-day**, multicenter (7 sites in Canada), placebo-controlled (**placebo H and L** as noted above for study 102-93-1), three-arm (all treatments were 40 drops QID) trial to "confirm" the safety and efficacy of Pennsaid for OA of the knee. This was a **non-flared study. The primary outcome variable was the WOMAC Likert 3.0 OA index pain scale score** from baseline to final assessment. Secondary variables included WOMAC stiffness, physical function and patient global as well as the daily global comparison noted above for trial 102-93-1. **Approximately 50% of the patients had both knees treated although only one was assessed for efficacy.**

The protocol initially called for 150 patients to be enrolled but this was increased to 248 (this was actually 267 patients but 19 were considered screening failures) after it was discovered **"there arose some confusion among the investigators about the need for a proper baseline WOMAC pain assessment after washout** in those patients using an oral NSAID". This change of protocol of mixing non-flared and flared patients resulted

in the large differences between the number of randomized (N = 267) patients and those considered by the Sponsor to be the "All Treated" population (N = 248), the "Expanded-Treated Patients-ETP" population (N = 247), the ITT population (N = 170), the "restricted" ITT (N = 162) and the "per protocol" population (N = 88).

Using the Sponsor's definitions above and their analysis of results, it was noted that one-way and two-way ANOVA for all the populations noted above revealed significant differences ($P < 0.05$) in favor of Pennsaid compared to the placebo groups for WOMAC pain. Results also noted statistically significant differences of Pennsaid over controls for WOMAC stiffness and physical function (11 of 12 comparisons) and in the patient global (3 of 6 comparisons). However, there was no statistically significant difference from control or placebo in the analysis of the daily global comparison.

> ***Reviewer's comment:*** *The Sponsor classified those patients that had both baseline and final efficacy assessments as the ITT population, this differs from the usual FDA definition in that the final assessment is not included. The mix of patients in the protocol between non-flared and flared with subsequent removal of 77 patients because they had no baseline "flare" data is problematic even if outlined "before blind breaking" as argued by the Sponsor since it seriously confounds interpretation of the trial results.* ***This was a poorly conducted trial whose results can only be used to suggest efficacy of Pennsaid and how not to conduct further trials. There was no stratification for patients as to the number of joints treated in each patient. It is of interest to note that 50% of patients had both knees treated. Furthermore, its short duration is of insufficient length to support being considered a pivotal trial. The FDA statistician did not reanalyze any of the data from this trial.***

Trial Design of Pivotal Studies:

Studies 109 and 109-US were as titled as follows by the Sponsor:

RA-CP-109 (study 109)
"A Double Blind, Placebo-Controlled, Two-way Parallel Clinical Trial to **Confirm** the Safety and Efficacy of PENNSAID® in the **Treatment of the Osteoarthritic Knee**"

RA-CP-109-US (study 109-US)
"A Double Blind, Vehicle-Controlled, Two-way Parallel Clinical Trial to **Confirm** the Safety and Efficacy of PENNSAID® Topical lotion in the **Treatment of the Osteoarthritic Knee**"

> ***Reviewer's comment:*** *Since studies 109 and 109-US are similar, they will be discussed together in this review unless otherwise noted. It is interesting to note*

*that in the title of both protocols it is stated "to **Confirm the Safety and Efficacy**" since this had not been established when these protocols were written. It is also of note that both protocols state "**Treatment of the Osteoarthritic Knee**", not of knees. Also, trial 109 is considered a "**Placebo-Controlled**" trial while 109-US is a "**Vehicle-Controlled**" trial when the treatments and controls were the same in both trials.*

Table 3 compares some of the essential features of study 109 and 109-US.

Table 3: Adequate and Well-Controlled trials in NDA 20-947

Protocol No. (RA-CP)	No. of Sites[1] Country Start Date	Study Design (Duration of Treatment	Treatments[2]	No. Patients[3] (Pennsaid/DMSO) Mean Age Range of Ages
109	17 Sites Canada 11/29/1999	Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Groups (6 weeks)	**Pennsaid:** 1.5% diclofenac + DMSO **DMSO:** 45.5% dimethyl sulfoxide — propylene glycol — ethyl alcohol — glycerine	**216** (107/ 109) 65 yrs 40-85
109-US	40 sites United States 12/19/2000	Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Groups (12 weeks)	**Pennsaid:** 1.5% diclofenac + DMSO **DMSO:** 45.5% dimethyl sulfoxide — propylene glycol — ethyl alcohol — glycerine	**326** (161/162) 63 42-85

b(4)

1. For study 109-US, the Sponsor has listed (Synopsis, original paper NDA, unpaginated document) 43 investigators, however, 3 of the investigators were at the same site.
2. The Sponsor states that 40 drops of either Pennsaid (which is the DMSO control with diclofenac) or DMSO were applied each time. ***Medical Officer Note:** Depending on the location in the NDA material submitted, this number of drops is either = 1 mL (Unnumbered Table: synopsis for both trials) or 1.4 mL (unnumbered Table entitled 'Table of All Controlled Clinical Studies': section 'D-E Tables' from Word documents submitted with original NDA). This 40% error may have important long-term consequences (see Table 8, Exposures with Pennsaid Use).*
3. The number of patients listed here are those of the FDA Medical Officer and Statistician since they differ from the number reported by the Sponsor.

Table 4 (from Table 3, page 49, Study RA-CP-109-US) summarizes the basic protocol that was followed for both studies 109 and 109-US with the latter serving as the example. Each protocol had a screening visit, a washout to allow a flare of the patient's OA after medications were removed before the baseline visit (for randomization and entry into the trial), and a final assessment at the end of the study or at the time of dropout. Visits, either at the clinic, or by telephone, were conducted at intervals between the baseline and end-of-study visit. **Efficacy was assessed only twice during the trial (baseline and end of study). The primary difference between study 109 and 109-US was in the length of treatment (109-six weeks; 109-US-twelve weeks) and the time between visits.**

Table 4: Study RA-109-US: Design and Schedule of Assessments

	Screen		Treatment Period					
Visit	S		B	1C	3T	6C	9T	12C7 Final
Interval from previous visit			see Appendix II	1 week	2 weeks	3 weeks	3 weeks	3 weeks
Consent	X							
Inclusion/Exclusion	X		X					
Randomization			X					
Pregnancy Test (if appropriate)	X							X
Medical & Medication History	X							
Physical Examination	X							
Vital Signs	X		X					X
X-rays	X*							
Blood Draw for PK analysis (subset)			X					X
Study Medication Dispensed			X			X		
Study Medication Returned						X		X
Booklet Dispensed			X					
Completed Booklet Returned								X
WOMAC assessment			X					X
Patient Global Assessment			X					X
Adverse Event Evaluation				X	X	X	X	X
Skin Irritation				X		X		X
Concomitant Medication				X	X	X	X	X

Washout Period

** If not done in the previous 3 months

Reviewer's Comment: *Table 4 is not completely accurate in that WOMAC pain was assessed in both protocols at the screening visit.*

Every patient was **screened** for eligibility (see inclusion/exclusion criteria below). After the screening interview, the patient had a 3-14-day washout (discontinuing all prohibited medications and therapies, including acetaminophen) prior to the **baseline visit** at which the patient must have experienced a **moderate "flare"** of knee pain. Washout was repeated if the patient used any prohibited medications during this time. **Flare was defined with the use of the WOMAC index at 48 hours** (see 'Endpoints') as **all** of the following **in the target knee:**

- Score of at least 2 (moderate) on at least one of the five items on the WOMAC Likert pain subscale (i.e. none = 0, extreme = 4).
- Baseline WOMAC pain subscale score ≥ 6 (20 possible)
- Increase in WOMAC pain subscale score from baseline to screening of 2 or 25% (which ever is greater)

If both knees were involved and found to qualify for inclusion, the knee with the higher baseline pain score was selected. If the pain scores where the same for both knees, the dominant knee was chosen for study.

Once randomized to the study, each patient applied **40 drops (1.0 or 1.4 mL,** the estimated volume that 40 drops of Pennsaid equalled changed repeatedly throughout the NDA) of study lotion. The instructions were to apply Pennsaid **four times a day** to the front, back, medial and lateral sides of the study knee (resulting in approximately **60 mg of diclofenac/day applied per knee**; see Table 22, Exposures with Pennsaid use).

> ***Reviewer's comment:*** *According to the Sponsor,* ***no clinical data justified the regimen of 4 times a day.*** *It was based on the clinical experience of the patent developer who used the product under the provisions of extemporaneous compounding. A pre-clinical study demonstrated that percutaneous penetration of diclofenac was enhanced by multiple applications of PENNSAID, so the timing for application of study lotion was linked to various daily activities in order to facilitate patient compliance with the four-times-a-day regimen, i.e., upon rising or after bathing in the morning, lunch time, dinner time and before going to bed in the evening. There was no presumed pharmacological relationship to meals.*
>
> *According to the sponsor, the initial choice of 1.5% diclofenac sodium was based, in part, on what was available in Europe* ***(Voltaren Emulgel - 1.16% diclofenac*** *diethylammonium salt, used 3-4 times daily).*

The investigator gave the patient instructions on how to apply the lotion to his/her study knee - **10 drops to each side, 5 drops at a time to avoid spillage,** directly to the knee or first onto the patient's hand, and then spread over the side. This was repeated for all four sides of the study knee, left side, right side, back side and front side of knee (and, if needed, the non-study knee as well). The patient then applied the first dose in the clinic, under observation. The lotion left the area visibly wet for several minutes, and was applied **without massaging** (massaging was proscribed to eliminate its possible therapeutic benefit).

Since **this was an outpatient trial,** the patient was then given a **booklet** (with the target knee identified by the investigator), 5 bottles of **study lotion** and 1 bottle of 50 x 325 mg **acetaminophen tablets as rescue medication.** The patient was reminded not to take any rescue acetaminophen during the final week of treatment. The patients were also reminded at each opportunity .by the investigator (according to the protocols) that lack of compliance or not properly notifying the investigator after they dropped out that 'without this information, all of his/her effort in the study would have been wasted'.

> ***Reviewer's comment:*** *The sponsor notes that where there was pain in the other knee, both knees were treated with study lotion, but only the more severely-*

affected knee, based on WOMAC pain dimension baseline assessment, was included for statistical evaluation. Both treated knees were assessed for safety. ***The differing use of Pennsaid in these trials and its major implications for interpretation of the study results (i.e. whether more than one knee was treated during the study) is of concern since there was no stratification strategy discussed for such analysis and execution of either pivotal trial.*** *The frequent reminders to patients regarding the need to be compliant with the protocol may help to account for the high compliance rates noted in these protocols (see table below).*

Follow-up **telephone'visits'** were interspersed with clinic visits (see Table 3). During the call, the investigator confirmed that the patient was applying the lotion properly. The investigator inquired about any adverse events and recorded them on a CRF. For any significant event, the investigator asked the patient to come into the clinic for a confirmatory visit. Such **significant events included redness with edema, vesicle or blister formation at the application site, wheezing, hives or similar allergic systemic reaction, and GI bleeding.** At this 'confirmatory clinic visit', the investigator documented all of the details of the AE on the CRF.

Reviewer's comment: *In the protocols, the investigator reminded the patient at both the telephone and clinic visits that if the non-study knee were to become painful at any time during the treatment period, the patient should apply study lotion to that knee in the same dose and frequency for the duration of the study. The purpose of this extra treatment was to minimise the need for supplemental rescue analgesia. The date of instituting treatment on the second knee was entered into the booklet and passed on to the study coordinator at the next visit. According to the Sponsor, this information was necessary to determine both demographic data and extent of exposure to study lotion.* ***Unfortunately, although this approach may mimic clinical practice, it does not allow robust assessment of efficacy.***

At clinic visits, the patient was assessed for problems with application of the study lotion or any other aspect of the study. The safety evaluation was completed which included assessment of the application site, inquiry regarding new adverse events (see questionnaire, Safety review) since the last telephone visit and resolution of any AEs previously reported. The previously dispensed booklet and bottles of study lotion and acetaminophen, whether used or not, were collected or accounted for. The study lotion bottles were weighed and acetaminophen tablets were counted and details recorded on a CRF. The booklet was reviewed to determine if the patient had treated the non-study knee, as well. The booklet was returned to the patient. If the questionnaire had been answered in error, the booklet was replaced.

The patient then received new bottles of study lotion, acetaminophen tablets and the patient was advised to continue application of the study lotion four times daily. The patient was advised to bring all medications (study lotion and acetaminophen) and the booklet to the next and final visit. The patient was also reminded to discontinue use of acetaminophen for one week before the final visit.

At the **final clinical visit (end of study or drop-out, see below),** the patient was assessed regarding compliance and AE monitoring. The booklet was reviewed to determine if the patient had treated the non-study knee, as well. If the questionnaires had not yet been answered, the booklet was returned to the patient so that a final assessment could be completed immediately.

Patients dropped out of the study prematurely, were instructed to complete the patient booklet including the final assessment questionnaires and book a final/termination visit. When the patient attended the final/termination, all procedures for 'Final' were followed. including entering the reason for dropping out of the study. If the reason for drop out was an AE, the investigator and/or delegate followed up on this event and to ensure appropriate patient care and follow up until resolution of the adverse event.

Concomitant medications:
In general, patients were allowed to continue taking non-analgesic, non-anti-inflammatory medication or other treatment for non-arthritic conditions. At each subsequent visit, clinic or telephone, the investigator inquired about any new concomitant therapy added since the previous visit and entered the information on the appropriate CRF. Patients were allowed to take non-analgesic doses of ASA (up to 325 mg/day) for cardiovascular prophylaxis throughout the study.

For "humanitarian reasons" if required for relief of pain, patients were **allowed to take acetaminophen tablets (325 mg tablets, QID),** if necessary, during the Treatment Phase of the study **for the relief of OA pain.** Patients were also prohibited from taking any acetaminophen tablets for three days prior to the final assessment, but this could not be enforced. Patients were supplied with acetaminophen tablets but there was no instruction on their use to relieve pain.

> ***Reviewer's comment:*** *The Sponsor stated that the control-DMSO group would be more likely to drop out because of inadequate relief of pain. This differential loss would reduce the size and hence the power of the per patient group analysis to determine the therapeutic advantage of PENNSAID. Although all such dropouts would still be included in the ITT analysis, it was hypothesized by the Sponsor that patients in those groups would be more likely to have used acetaminophen in the week prior to final assessment and that this analgesic effect could influence the ITT data, biasing against PENNSAID.*

Inclusion criteria:

According to the Sponsor, to be **included** in these trials, patients had to:

- Be between 40 and 85 years of age
- Have signed an informed consent after the nature of the study was explained to them
- If female, be unable to become pregnant (surgically sterile or postmenopausal for 6 months) or not pregnant with a negative pregnancy test within 48 hours of screening and using an

acceptable method of contraception (including oral contraceptives, IUDs, spermicide with a barrier or male sexual partner/s surgically sterile).

- Be taking an NSAID or other analgesic on a regular basis (i.e. at least 3 days per week for 1 month) prior to the screening visit with a flare (see above) after its discontinuation.
- Be in reasonably good health, except for OA.
- Have primary OA of the knee/s characterised by deterioration and abrasion of articular cartilage (joint space narrowing) and/or formation of new bone at the joint surface (osteophytes). Radiographs of the knees included antero-posterior (standing or supine), lateral and axial (skyline, sunset, sunrise) views. Osteoarthritis of the knee was characterized by marginal osteophytes, joint space narrowing and subchondral sclerosis in the tibiofemoral lateral or medial compartment and the patellofemoral compartment according to standard radiological criteria (Altman Atlas).

Exclusion criteria:

According to the Sponsor, a patient was **excluded** from the study if s/he met any of the following criteria:

- Patient selection was consistent with all warnings, precautions, and contraindications stated in the current product monograph or package insert for oral diclofenac.
- Known sensitivity to the use of diclofenac, DMSO, glycerine, propylene glycol, ethanol, ASA or any other NSAID. This included any patient exhibiting aspirin or other NSAID-induced bronchospasm, rhinitis, urticaria, or other allergic symptoms.
- Severe, uncontrolled cardiac, renal, hepatic or other systemic disease.
- Any patient with a documented (UGI series or endoscopy) gastro-duodenal ulcer or any gastrointestinal bleeding (except hemorrhoidal) within the last six months was excluded.
- Systemic disease that may have affected bone or joints including psoriasis, syphilitic neuropathy, ochronosis, chondrocalcinosis, metabolic or other primary bone disease or acute trauma only if there was evidence of that disease in the study knee, such that the development of symptoms in the knee might confuse the interpretation of the clinical response of the patient's osteoarthritis to study therapy.
- Previous major damage or major surgery to the knee at any time (including damage/reconstruction of the anterior or posterior cruciate ligaments. Any patient who had undergone minor knee surgery within the last year.
- Documented history of alcohol or drug abuse within one year prior to study entry.
- Nursing mothers.
- Corticosteroids required orally or topically at the study knee or IA injection with 90 days of entry or any joint within 30 days.
- Use of viscosupplements (i.e. Synvisc) in the study knee in the preceding 3 months.
- Use of prohibited concomitant medications/therapies to include oral NSAID (selective or non-selective), including over-the-counter ASA, ibuprofen and naproxen, muscle relaxants, other oral analgesics (prescribed or over-the-counter), or antidepressants prescribed for the control of chronic pain syndromes, topical products on the knee including methyl salicylate, camphor, menthol or capsicum, any non-pharmaceutical therapy or device to relieve knee pain (including physiotherapy, massage therapy, hot wax therapy etc.), methylsulfonylmethane, glucosamine, chondroitin (these latter two were allowed if started within 90 days of baseline), and anti-depressants started during the study. Concomitant medications or other treatments were not used except as approved by the investigator.
- Could not tolerate acetaminophen.

- Had previously been enrolled in any trial involving PENNSAID Topical Lotion.
- Had been in another investigational drug trial within the previous 30 days.
- Applying for disability benefits on the basis of knee osteoarthritis.
- Fibromyalgia was excluded.
- With other painful or disabling conditions affecting the knee or leg.
- With a skin disorder with current involvement of the knee(s).
- Referred to an orthopedic surgeon for or advised to have knee replacement or knee reconstruction surgery
- Severe osteoarthritis of the knee.

Baseline Demographics:

The baseline demographics of the patients as originally enrolled in studies 109 and 109-US are noted in **Table 5.**

Table 5: Baseline Demographics: Studies 109 and 109-US

	Pennsaid	DMSO
Study 109[1]		
Age (yrs)		
N	107	109
Mean	65.0	64.6
Range	40-85	40-85
Gender (% of N)		
Female	56	61
Male	44	39
Race (%)		
Caucasian	88 (82)	91 (84)
Black	8 (7)	3 (3)
Asian	3 (2)	2 (2)
Other	8 (8)	13 (12)
Study 109-US		
Age (% of N)		
N	164	162
Mean	63.4	64.0
Range	42-85	41-84
Gender (%)		
Female	69	67
Male	31	33
Race (%)		
Caucasian	142 (87)	148 (91)
Black	18 (11)	12 (7.4)
Asian	1 (< 1)	0
Other	3 (2)	2 (1)

1. From Table 15, RA-CP-109. Number of patients are according to the Sponsor (Table 6 below).
2. From Table 15, RA-CR-109-US. Number of patients are according to the Sponsor (Table 6 below).

Reviewer's comment: *This table only notes comparisons across the treatment groups, not the treatment arms (i.e. one, two or both knees, see below). As noted below, the Sponsor considered for their statistical and clinical evidence for efficacy of Pennsaid that only two groups existed i.e. Pennsaid and DMSO.*

However, upon review of the data as discussed earlier, it became clear that actually the treatment groups consisted of Pennsaid or DMSO that was used to treat only 1 knee with OA for the duration of the study, 2 knees for the duration of the study, or both knees for differing times during the study. This variability of treatment has a limiting effect on the ability to draw statistically rigorous conclusions regarding the efficacy of Pennsaid from this NDA. The designation of patients into these three treatment arms (i.e. 1 knee, 2 knee, both knees) for Pennsaid and DMSO forms the essence of this remainder of this review.

Patient Disposition:

As noted earlier, patients were not treated uniformly (i.e. one knee or two knees treated and assessed) during studies 109 and 109-US. **Table 6** categorizes the number of ITT patients according to the Sponsor's definition of the data. As can be seen, **most of the patients had two knees treated for both studies.**

Table 6: Number of Patients (ITT) in NDA 20-947 OA trials: Sponsor data[1]

	RA-CP-109 (% of N)			RA-CP-109-US (% of N)		
	Penn	DMSO	Total	Penn	DMSO	Total
1 knee only	22 (10)	18 (8)	40 (18)	38 (11)	33 (10)	70 (22)
2 knee only	63 (29)	68 (32)	131 (61)	101 (31)	33 (10)	210 (65)
Both knees	22 (10)	23 (11)	45 (21)	23 (7)	19 (6)	42 (13)
Total	107 (50)	109 (50)	216 (100)	161 (50)	162 (50)	326 (100)

1 From line listings and table (unnumbered), attachment 1 (no pagination), response to Clinical Request for Information, April 3, 2002 (no serial number).

Reviewer's comment: *Neither protocol for study 109 or 109-US addressed the issue of stratifying patients based upon whether they were going to have one, two or a combination of both, knees treated during the trial as noted above. Unfortunately, the patients who ended up in the three treatment arms noted in Table 6 did not get there by valid randomization techniques rendering conclusions about efficacy unreliable. In addition, it has resulted in unbalanced, and also underpowered treatment groups which limits the robustness and accuracy of any conclusions regarding efficacy.*

Also, comparisons of some of the bolded numbers in this table with the next table will give an example that raises concern about the data submitted for NDA review.

Table 7 notes the number of ITT patients according to the review of studies 109 and 109-US by both this reviewer and the FDA statistician. Again, most patients had two knees treated during both studies.

Table 7: Number of Patients (ITT) in NDA 20-947: MO review of data[1]

	RA-CP-109 (% of N)			RA-CP-109-US (% of N)		
	Penn	DMSO	Total	Penn	DMSO	Total
1 knee only	23 (11)	18 (8)	41 (18)	37 (11)	33 (10)	70 (22)
2 knee only	63 (30)	75 (35)	138 (65)	100 (31)	110 (34)	210 (65)
Both knees	19 (9)	15 (7)	34 (16)	24 (7)	19 (6)	43 (13)
Total	105 (49)	108 (51)	213 (100)	161 (50)	162 (50)	323 (100)

1 From line listings and table (unnumbered), attachment 1 (no pagination), response to Clinical Request for Information, April 3, 2002 (no serial number).

The number of patients who completed the trial, defined by this reviewer as having completed 40 days (study 109) or 80 days (109-US) or more of treatment with either Pennsaid or DMSO are listed in **Table 8**. There was a trend to more completers in the Pennsaid vs. the DMSO treatment groups, although there was no difference between the 2 knee-treated patients in study 109-US. With each treatment group, the length of the study (i.e. 6 weeks for 109 and 12 weeks for 109-US) did not seem to influence the rate of completion.

Table 8: Number of Patients (completers) in NDA 20-947 OA: MO review of data[1]

	RA-CP-109 (% of N)			RA-CP-109-US (% of N)		
	Penn	DMSO	Total	Penn	DMSO	Total
1 knee only	17 (11)	11 (7)	28 (18)	26 (12)	20 (9)	46 (20)
2 knee only	51 (33)	47 (30)	98 (63)	72 (32)	72 (32)	144 (64)
Both knees	17 (11)	12 (8)	29 (19)	21 (9)	14 (6)	35 (16)
Total	85 (55)	70 (45)	155 (100)	119 (53)	106 (47)	225 (100)

1 From line listings and table (unnumbered), attachment 1 (no pagination), response to Clinical Request for Information, April 3, 2002 (no serial number). Completers were defined as those patients who had treatment for ≥ 40 days (RA-CP-109) or ≥ 80 days (RA-CP-109-US).

The percent of patients that completed study 109 and 109-US are listed in **Table 9** based upon whether one or two knees were treated. There appears to be a greater compliance when 2 (vs. 1) knees are treated and when Pennsaid (vs. DMSO) is applied.

Table 9: Percent of patients completing treatment in NDA 20-947

	Study RA-CP-109		Study RA-CP-109-US	
	Pennsaid	DMSO	Pennsaid	DMSO
2 knees	81	63	72	65
1 knee	74	61	70	61

The number of patients classified as the ITT population and the completers population are summarized in **Table 10** below.

Table 10: ITT and completers patients: RA-CP-109 and RA-CP-109-US)[1]

	ITT (% of N)			Completers (% of N)		
	Penn	DMSO	Total	Penn	DMSO	Total
1 knee only	60 (11)	51 (10)	111 (21)	43 (11)	31 (8)	74 (19)
2 knee only	163 (30)	185 (35)	348 (65)	123 (32)	119 (31)	242 (64)
Both knees	43 (8)	34 (6)	77 (14)	38 (10)	26 (7)	64 (17)
Total	266 (50)	270 (50)	536 (100)	204 (54)	176 (46)	380 (100)

1 From line listings and table (unnumbered), attachment 1 (no pagination), response to Clinical Request for Information, April 3, 2002 (no serial number). Patients are defined per MO review of sponsor data.

For comparison, the number of patients in the ITT and completer populations in study 107-96 are noted in **Table 11.**

Table 11: Number of Patients (ITT and completers): study 107-96[1]

	ITT (% of N)				Completers (% of N)			
	Penn	DMSO	Placebo	Total	Penn	DMSO	Placebo	Total
1 knee only	51 (21)	41 (17)	42 (17)	134 (54)	47 (22)	35 (16)	34 (16)	116 (53)
2 knee only	31 (13)	36 (15)	39 (16)	106 (43)	28 (13)	32 (15)	36 (17)	96 (44)
Both knees	2 (1)	2 (1)	4 (1)	8 (3)	2 (1)	1 (0)	2 (1)	5 (2)
Total	84 (34)	79 (32)	85 (34)	248 (100)	77 (35)	68 (31)	72 (33)	217 (100)

1 From line listings and table (unnumbered), attachment 1 (no pagination), response to Clinical Request for Information, April 3, 2002 (no serial number). Patients are defined per MO review of sponsor data. DMSO = 45%. Placebo = 4.5% DMSO.

A detailed accounting for patient disposition based upon treatment and study outcome in study 109 is noted in **Table 12.**

Table 12: Study RA-CP-109: Patient by treatment and outcome-Sponsor data[1]

Group	**Primary efficacy outcome**		
	WOMAC pain	WOMAC function	Pt Global
Pts screened	**411**	**411**	**411**
-screen failures[2]	195	195	195
All Treated Pts[3]	**216**	**216**	**216**
-Failed ITT Criteria: ———	15	15	16
-Invalid Baseline Assessment	2	4	4
-Invalid Final Assessment	9	6	7
-No Radiological Evidence of OA	2	2	2
-Patient Does Not Have Primary OA	2	3	3
Modified Intent to Treat	**201**	**201**	**201**
-Add'l failed ITT Criteria: per Sponsor	7	7	7
-Invalid Baseline Assessment	1	1	1
-Invalid Final Assessment	6	6	6
Intent to Treat	**194**	**194**	**193**
-Failed Per Protocol Criteria:	66	67	66
-less than 40 days of treatment	42	44	43
-Use of prohibited medication (including APAP) 1 week prior to final assessment	14	14	14
-No moderate flare of pain prior to entry	10	9	9
Per Protocol	**128**	**127**	**127**
Completers	**156[5]**		
	Pennsaid	**DMSO**	
Total	**107**	**109**	
-completed	**86**	**70**	
-withdrawn	**21**	**39**	
-pre-existing entry criteria violation	1	2	
-protocol violation	0	3	
-lack of effect	8 (38%)	18 (46%)	
-adverse event	9 (43%)	9 (23%)	
-other	3	7	

b(4)

1. From Figure 1 (not paginated) of Word document (109-01-10 intro) submitted with original NDA.
2. Screening failures were primarily driven by pt with no evidence of OA (8%), pt did not flare (47%) and pt could not tolerate pain during washout period (16%).
3. **Medical officer note: This 'All Patients Treated' population (although it differs from that of the reviewer's Table 3 , i.e. N = 213) is considered the ITT population in the remainder of this review.**
4. ——— to the Sponsor.
5. **Medical officer note: The numbers of completers differs from those in reviewer's Table 5 (N = 155).**

b(4)

Reviewer's comment: *It is of concern that the Sponsor's ITT population (N = 193-194 depending on outcome of interest) differs significantly from this reviewer's and the statistician's (see review, Suktae Choi PhD) with N = 213. (see Table 3).*

A detailed accounting for patient disposition based upon treatment and study outcome in study 109-US is noted in **Table 13.**

Table 13: Study RA-CP-109-US: Patients by treatment and outcome-Sponsor data[1]

Group	**Primary efficacy outcome**		
	WOMAC pain	**WOMAC function**	**Pt Global**
Pts screened	**568**	**568**	**568**
-screen failures[2]	242	242	242
All Treated Pts[3]	**326**	**326**	**326**
-Failed ITT Criteria	49	50	51
-Invalid Baseline Assessment	0	1	2
-Invalid Final Assessment	40	40	40
-Patient Does Not Have Primary OA	1	1	1
-Use of Prohibited Medication	2	2	2
-Protocol violation	6	6	6
Intent to Treat	**277**	**276**	**275**
-Failed Per Protocol Criteria:	106	105	106
-Less than 83 days of treatment	87	87	87
-Use of prohibited medication	7	7	7
-No moderate flare of pain prior to entry	5	4	5
-Protocol violation	7	7	7
Per Protocol	**171**	**171**	**169**
Completers	**228[4]**		
	Pennsaid	**DMSO**	
Total	**164**	**162**	
-completed	**119**	**109**	
-withdrawn	**45**	**53**	
-pre-existing entry criteria violation	0	0	
-protocol violation	0	1	
-lack of effect	28 (17%)	42 (26%)	
-adverse event	8 (5%)	3 (2%)	
-other	9	7	

1 From Figure 1 (not paginated) of paper copy (Section10.1) of original NDA.

2 Screening failures were primarily driven by pt with no evidence of OA (24%), pt did not flare (26%), pt had existing medical condition and/or procedure (13%), and pt did not wish to continue (14%).

3 **Medical officer note: this 'All Patients Treated' population (although it differs from that in the reviewers Table 3, i.e. N = 323) is considered the ITT population in the remainder of this NDA review.**

4 **Medical officer note: The number of completers differs from those in reviewer's Table 5 (N = 225).**

Reviewer's comment: *It is of concern that the Sponsor's ITT population (N = 275-277 depending on outcome of interest) differs so significantly from this reviewer's and the statisticians (see review, Suktae Choi PhD) of N = 323 (see Table 3).*

Efficacy Assessment:

As noted in the OA guidance document (draft, 1999), the **primary outcome measures in OA include patient pain, physical function and patient global.** All three must be statistically significant at $p < 0.05$, there are no adjustments for multiple comparisons.

The **Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index** is a segregated multidimensional, self-administered index with three independent dimensions; **pain,** stiffness and **physical function.** It is a highly validated, reliable and responsive outcome measure for OA of the knee or hip. Scoring of the WOMAC Osteoarthritis Likert 3.1 index used in these protocols ranged from 0 = none to 4 = extreme with a total score of 20 for pain and 68 for function.

The WOMAC index is as follows:

INSTRUCTIONS TO PATIENTS

In Sections A, B and C, questions will be asked in the following format.
You should give your answers by putting an " X " in one of the boxes.

EXAMPLES:

1. If you put your "X" in the left-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
☒	☐	☐	☐	☐

Then you are indicating that you have no pain.

2. If you put your "X" in the right-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☒

Then you are indicating that your pain is extreme.

3. Please note:
   a) that the further to the right you place your "X" the more pain you are experiencing.
   b) that the further to the left you place your "X" the less pain you are experiencing.
   c) please do not place your "X" outside the box.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.
Think about your ..... (study joint) when answering the questionnaire.
Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your ..... (study joint).
Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

YOU MUST COMPLETE ALL OF THESE QUESTIONS when you have finished the study or if, for any reason, you drop out of the study. If you do not answer the questions, your efforts and participation in the study will have been wasted.

WOMAC Osteoarthritis Index LK3.1

Section A

PAIN

Think about the pain you felt in your _____ (study joint) due to your arthritis during the last 48 hours.

(Please mark you answers with an "X ".)

QUESTION: How much pain do you have?

1. Walking on a flat surface.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

2. Going up or down stairs.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

3. At night while in bed. i.e., pain that disturbs your sleep.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

4. Sitting or lying.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

5. Standing upright.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your ..... (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself.

(Please mark you answers with an "X ".)

QUESTION: **What degree of difficulty do you have?**

8. Descending stairs.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

9. Ascending stairs.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

10. Rising from sitting.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

11. Standing.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

12. Bending to the floor.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

13. Walking on a flat surface.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

QUESTION: What degree of difficulty do you have?

14. Getting in or out of a car, or getting on or off a bus.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

15. Going shopping.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

16. Putting on your socks or stockings.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

17. Rising from bed.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

18. Taking off your socks or stockings.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

19. Lying in bed.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

QUESTION: What degree of difficulty do you have?

20. Getting in or out of the bath.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

21. Sitting.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

22. Getting on or off the toilet.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

23. Performing heavy domestic duties.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

24. Performing light domestic duties.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

The Patient Global Assessment was a five-point categorical scale (very good = 0 to very poor = 4) in which the patient was asked to give and overall assessment of the study knee to the following question, 'How has the osteoarthritis in your (target) knee been over the last 48 hours?'

> ***Reviewer's comment:*** *This patient global question is merely another efficacy assessment, not one intended to capture the patients overall experience with the test lotion.*

Secondary Efficacy Variable
The secondary efficacy variable was the change in the WOMAC LK3.1 stiffness dimension score from the baseline to final assessment, as compared with baseline score.

WOMAC Osteoarthritis Index LK3.1
Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your (study joint) due to your arthritis during the last 48 hours.
Stiffness is a sensation of decreased ease in moving your joint.

(Please mark you answers with an "X ".)

6. How severe is your stiffness after first awakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. How severe is your stiffness after sitting, lying or resting later in the day?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Statistical issues:

Interim analysis
No interim analysis or monitoring of the results of these studies was planned. However, according to the sponsor, for study 109 an unplanned analysis (of the WOMAC pain of the first 60 patients) was conducted to verify and assess the appropriateness of the variability estimate used to calculate sample size (see below) since this had been derived from study 107-96 which was a non-flare design study (see description of this trial above). No hypothesis testing or efficacy evaluation was performed. No adjustments were made to the sample sizes from these calculations.

Primary Efficacy Variable Analysis
The three primary endpoints included the change in WOMAC Pain, WOMAC Physical Function and Patient Global Assessment score from baseline to final assessments. The efficacy analysis sets included the intent-to-treat (ITT) and per protocol groups in both

protocols and the modified ITT in protocol ~~109,~~ conclusions were to be based on the ITT population. **Both primary and secondary (i.e. WOMAC stiffness) endpoints used ANCOVA,** with baseline score as a covariate of the overall treatment effect. All tests were two-sided at the 5% level of significance with no adjustments. Centers were to be combined for analysis.

> ***Reviewer's comment:*** *The three primary and secondary endpoints only had baseline and landmark, or end-of-study values. There where no other efficacy assessments made in both studies so it is not possible to get an idea as to onset or directionality of patient response to the two treatments as the study moved along. To help address Pennsaid's efficacy, it would be useful to know whether the responses seen were improving, stable or decreasing toward the end of these studies.*

The ITT population in both studies was defined by the Sponsor as all patients who satisfied all major entry criteria (based on inclusion/exclusion criteria), had at least one dose of study medication and had valid baseline and final data. The per protocol population included patients from the ITT population who demonstrated 'greater compliance with the protocol.' In particular, this meant that the patients must have been treated for at least 83 days for study ~~109-US~~ and 43 day for study ~~109~~. **In study ~~109,~~ the sponsor identified a modified ITT (Table 12) which was defined following blind-breaking which essentially included patients that had originally been excluded from analysis by the Sponsor; this was based on advise of an outside statistician.**

> ***Reviewer's comment:*** ~~***The sponsor's definition of ITT is unacceptable.***~~ ***It differs from that normally applied to studies reviewed by FDA*** *(i.e. ITT = patients who were randomized, had a baseline assessment, and received one dose of study medication). It is of note that the "completer" population selected by both this reviewer and the FDA statistician (Table 8) did differ, but not substantially, from the "per-protocol" population noted by the sponsor (Tables 12 and 13).*

Missing Data

Missing data for the WOMAC pain subscale were imputed from the average of the remaining completed items if the missing were ≤ 2 of 5 items. Up to three items were allowed to be missing and therefore imputed for the WOMAC physical function outcome.

> ***Reviewer's comment:*** *The way missing data is handled by the Sponsor differs from that noted in the WOMAC user's guide; for example, only one item is allowed to be missing for pain.*

Demographic and Baseline (Covariate) Variable Analysis

According to the protocols, differences between treatment groups were examined by Student's t-test, chi-square test or Fisher's exact test as appropriate, only for those

relevant variables for which 1) between group differences are clinically important and 2) the variable may affect the outcome.

When a statistically significant difference between treatment groups was confirmed, that variable was included as a covariate in the analysis of the efficacy results. Relevant variables included:

1. Male versus female
2. One versus two knees being treated
3. Age <75 versus age ≥ 75 years
4. Requirement of washout of previous medication prior to baseline
5. Severity of osteoarthritis based on knee X-ray score (normal=0, mild=1, moderate=2, severe=3; total score for three compartments). Severity of OA based on baseline pain score was already included as a covariant in the analysis of all efficacy variables
6. Prior use of other non-pharmacological treatment
7. Osteoarthritis of the back or hip(s)

Concomitant Medication
Descriptive statistics for concomitant medication (all taken orally or applied to the skin), by treatment group and/or study center, were examined by chi-square test or Fisher's exact test for those medications that may affect the outcome. If 'clinically relevant differences' were found between treatment groups, concomitant medication was to be included as a covariate in the analysis of primary efficacy data. Between group differences in acetaminophen 325-mg tablets use were examined by Student t-test. This difference was not be analyzed as an efficacy variable.

There was no intention to study any drug-drug interaction nor any drug-disease interaction other than the response to the study lotion.

Safety Variables
Statistical tests were two-sided at the 5% level of significance. Adverse events, expressed as incidence were analyzed by Chi-squared or two-tailed Fisher's Exact Test as appropriate. Skin irritation scores, based upon each patient's "worst" score at clinic visits, were analyzed by Mann-Whitney U test. A second analysis was performed using the "final" score (last valid observation) minus worst score, to evaluate whether the skin irritation improves despite continued use of PENNSAID. Scores were evaluated using the Chi-Square or Fisher's Exact test, as appropriate, comparing those patients whose worst skin irritation score occurred at the final visit and those whose skin irritation score improved with continued treatment. Change in vital sign data from baseline to final assessment was to be analyzed by Student t-test.

Determination of Sample Size:
The primary outcome variables were used to calculate sample size. For both study [redacted] and [redacted], from previous experience, the standard deviations were estimated to be 4.5 for the pain dimension, 15.0 for the physical function dimension and 1.0 for the patient global dimension. At an experimental power of 80% and a two-sided significance level of

0.05, each treatment group required 80 evaluable patients for the pain dimension in order to detect a 'clinically important difference' (CID) of 2.0; for physical function required 77 evaluable patients to detect a CID of 6.8 and 63 evaluable patients for the patient global to detect a CID of 0.5. The total sample size was based on the WOMAC pain dimension, a total sample size of 200 patients (100 per treatment group) was deemed necessary for enrollment to allow for a 20% loss.

Study 109-US				
Change in Primary Endpoint	SD Estimate	Clinically Important Difference	Evaluable cases/group	Total cases/group
WOMAC pain	4.5	2.0	80	100
WOMAC function	15.0	6.8	77	97
Pt global	1.0	0,5	63	79

History of protocol amendments:
Protocol amendments for **study 109-US** (originally submitted on November 13, 2000) included amendment 1 (November 29, 2000) before study initiation (December 19, 2000) and amendment 2 (June 20, 2001). Amendment 1 provided additional exclusion and safety criteria but did not affect monitoring, clinical efficacy requirements, alternative treatments or patient discontinuation, or result in the extension of the duration of the clinical trial. Amendment 2 included a revision to an exclusion criterion (i.e. excluding patients with intra-articular corticosteroid injections into any joint instead of any large joint) and it revised the washout of previous medication prior to baseline. In addition, it eliminated the statistical analysis of amount of rescue analgesia taken by the different groups and stated that rescue analgesia will be weighed instead of counted to assess use.

Study 109 was originally submitted to the Therapeutic Products Programme, Health Canada in September 1999. Amendments 1 and 2 occurred prior to study initiation and did not affect patient selection or monitoring, clinical efficacy or safety requirements, alternative treatments, patient discontinuation, or result in the extension of the trial. Amendment 3 (December 6, 2000) redefined treatment "on a regular basis" before screening and washout. Amendment 4 was made (September 8, 2000) which was after completion of the study (August 21, 1999) but before data lock (September 22, 2000). This amendment expanded the primary endpoints to include the WOMAC physical function and the Patient Global as primary outcomes (previously secondary).

Efficacy Results:

According to the Sponsor, ANCOVA with baseline scores as the covariate consistently revealed statistically significant differences ($p \leq 0$-.05) between treatment groups in favor of Pennsaid for all primary efficacy variables (i.e. WOMAC pain and physical function,

patient global) for both the ITT and per protocol population in both studies. **Table 14** summarizes the results for studies 109 and 109-US in NDA 20-947.

Table 14: NDA 20-947: Results with Primary Efficacy Variables-Sponsor [1]

Population[2]	Primary outcome variable[2]								
	Study RA-CP-109								
	WOMAC pain			**WOMAC function**			**Patient Global**		
	Total	Pennsaid	DMSO	Total	Pennsaid	DMSO	Total	Pennsaid	DMSO
mITT (n)	201	99	102	201	98	103	200	**97**[6]	**103**[8]
mean	-4.5	-5.6	-3.5	-10.4	-14.1	-6.9	-1.0[5]	**-13.0**[7]	-0.7
SD	**4.5**[3]	4.9	**4.3**[4]	15.3	16.4	13.3	**1.3**[5]	1.3	1.2
p-value		0.0025			0.0005			<0.0001	
ITT (n)	194	98	96	194	97	97	193	96	97
mean	-4.6	-5.6	-3.5	-10.7	-14.3	-7.2	-1.0	-1.3	-0.7
SD	4.7	4.9	4.2	15.2	16.4	13.1	1.3	1.3	1.2
p-value		0.0035			0.0009			**0.0001**[9]	
PP (n)	128	73	55	127	72	55	127	72	55
mean	-5.7	-6.6	-4.6	-14.1	-17.0	-10.4	-1.3	-1.5	-0.9
SD	4.5	4.5	4.3	15.1	15.7	13.5	1.2	1.2	1.2
p-value		0.0086			0.0064			0.0006	
	Study RA-CP-109-US								
ITT (n)	277	133	144	276	132	144	275	131	144
mean	-5.3	-6.4	-4.3	-13.4	-16.9	-10.2	-1.2	-1.4	-0.9
SD	4.8	4.8	4.5	15.3	15.7	14.1	1.2	1.2	1.2
p-value		0.0001			0.0003			0.0004	
PP (n)	171	88	83	171	88	83	169	86	83
mean	-6.5	-7.4	-5.5	-16.8	-19.6	-13.9	-1.4	-1.6	-1.2
SD	4.4	4.3	4.3	14.4	14.7	13.5	1.1	1.0	1.1
p-value		0.0045			0.0119			0.0163	

1 Table from Synopsis portion, 'Summary Conclusions' of unpaginated original NDA.

2 mITT = modified intent-to-treat: ITT = intent-to-treat; PP = per protocol. Mean values expressed as final-baseline; SD = standard deviation; p-values by ANOVA with baseline as covariate. N = number of patients. Endpoints as described elsewhere. Pennsaid = 1.5% w/w diclofenac with carrier solution including DMSO at 45.5%; DMSO = dimethyl sulfoxide at 45.5%.

3 Sponsor data Table 4 (ISE, unpaginated document, original submission) = 4.7.

4 Sponsor data Table 4 (ISE, unpaginated document, original submission) = 4.2.

5 Sponsor data Table 14 (ISE , unpaginated original submission) = no data listed.

6 Sponsor data Table 14 (ISE, unpaginated document, original submission) = 99.

7 Sponsor data Table 14 (ISE, unpaginated document, original submission) = -13.0.

8 Sponsor data Table 14 (ISE, unpaginated document, original submission) = 99.

9 Sponsor data Table 14 (ISE, unpaginated document, original submission) = 0.00010.0077.

Reviewer's comment: *The table demonstrates some examples of the inconsistencies in the Sponsor's data as which raises concerns about the integrity of the data. There were no center or treatment by center effects (two-way ANOVA, per sponsor) observed (i.e. $p \leq 0.05$) with any of the primary efficacy variables in the ITT or per protocol populations in either study. However, there was a center*

effect ($p < 0.0409$) for the ITT population for the secondary endpoint of study 109-US.

Table 15 summarizes the efficacy results for WOMAC pain for study 109 and 109-US as determined by the FDA statistician based upon the assignment of patients into the ITT populations as noted earlier. As can be seen, only the 2 knee-treated patients had statistically significant differences between treatment groups in favor of Pennsaid.

Table 15: WOMAC Pain: FDA-Statistical Comparisons (ITT) for NDA-20-947[1]

	Study RA-CP-109			Study RA-CP-109-US		
	N Mean (std dev)			N Mean (std dev)		
	Penn	DMSO	P-value	Penn	DMSO	P-value
1 knee only	N=23 -5.52 (4.54)	N=18 -3.44 (4.16)	0.0763	N=37 -6.11 (14.24)	N=33 -4.15 (4.27)	0.0873
2 knee only	N=63 -5.24 (5.34)	N=75 -3.15 (4.28)	0.02	N=100 -5.92 (4.73)	N=110 -4.40 (4.68)	0.0182
Both	N=19 -5.11 (4.34)	N=15 -5.20 (4.30)	0.95	N=24 -6.50 (4.59)	N=19 -4.84 (3.48)	0.1222
Total	N=105 -5.28 (4.96)	N=108 -3.48 (4.28)	0.0052	N=161 -6.05 (4.66)	N=162 -4.40 (4.45)	0.0008

1. Results refer to WOMAC physical function scores from FDA statistical review (Suktae Choi). P-values are from ANCOVA with factors of baseline and treatment groups as specified in the study protocols. Number of patients refers to those in the ITT population as defined by FDA re-interpretation of Sponsor's data (see Tables 7). One knee only refers to treatment of only the target knee. Two knees refers to treatment of the target AND non-target knee during the entire study. Both knees refers treatment of the target knee throughout the trial with the non-target knee treated at some point during the trial.

Table 16 summarizes the efficacy results for WOMAC pain for study 109 and 109-US as determined by the FDA statistician based upon the assignment of patients into the "completer" populations as noted earlier. Again, only the 2 knee-treated population shows significant treatment differences in favor of Pennsaid.

Table 16: FDA-Statistical Comparisons (completers) for WOMAC pain[1]

	Study RA-CP-109			Study RA-CP-109-US		
	N Mean (std dev)			N Mean (std dev)		
	Penn	DMSO	P-value	Penn	DMSO	P-value
1 knee only	N=17 -6.47 (4.36)	N=11 -4.27 (11.38)	0.1039	N=26 -7.38 (4.13)	N=20 -5.90 (3.46)	0.1024
2 knee only	N=51 -6.49 (4.94)	N=47 -4.09 (4.32)	0.0177	N=72 -7.08 (4.36)	N=72 -5.56 (4.57)	0.0568
Both	N=17 -5.71 (4.19)	N=12 -4.50 (4.32)	0.5317	N=21 -6.71 (4.58)	N=14 -6.21 (2.89)	0.681
Total	N=85 -6.33 (4.65)	N=70 -4.19 (4.34)	0.0036	N=119 -7.08 (4.32)	N=106 -5.71 (4.17)	0.0144

1 Results from FDA statistical review (Suktae Choi). P-values are from ANCOVA with factors of baseline and treatment groups as specified in the study protocols. Number of patients refers to those in the completers population as defined by FDA re-interpretation of Sponsor's data (see Tables 3).

Table 17 summarizes the efficacy results for WOMAC physical function for study 109 and 109-US as determined by the FDA statistician based upon the assignment of patients into the ITT populations as noted earlier. The results are similar to those for the ITT population analyzed for pain as noted above.

Table 17: FDA-Statistical Comparisons (ITT)-WOMAC Physical Function[1]

	Study RA-CP-109			Study RA-CP-109-US		
	N Mean (std dev)			N Mean (std dev)		
	Penn	DMSO	P-value	Penn	DMSO	P-value
1 knee only	N=23 -12.3 (12.98)	N=18 -6.67 (11.95)	0.1149	N=37 -14.78 (14.24)	N=33 -9.03 (13.59)	0.1174
2 knee only	N=63 -13.25 (18.08)	N=75 -6.68 (13.50)	0.0192	N=100 -16.13 (15.92)	N=110 -10.49 (14.75)	0.0081
Both	N=19 -13.32 (14.00)	N=15 -12.53 (14.33)	0.8112	N=24 -14.54 (14.22)	N=19 -11.47 (9.48)	0.4178
Total	N=105 -13.06 (16.27)	N=108 -7.49 (13.51)	0.004	N=161 -15.58 (15.23)	N=162 -10.31 (13.95)	0.0012

1 Results refer to WOMAC physical function scores from FDA statistical review (Suktae Choi). P-values are from ANCOVA with factors of baseline and treatment groups as specified in the study protocols. Number of patients refers to those in the completer population as defined by FDA re-interpretation of Sponsor's data (see Tables 4).

Table 18 summarizes the efficacy results for WOMAC physical function for study 109 and 109-US as determined by the FDA statistician based upon the assignment of patients into the "completer" populations as noted earlier. The results are similar to those in the same population noted above for pain.

Table 18: FDA-Statistical Comparisons (completers)-WOMAC Physical Function[1]

	Study RA-CP-109			Study RA-CP-109-US		
	N Mean (std dev)			N Mean (std dev)		
	Penn	DMSO	P-value	Penn	DMSO	P-value
1 knee only	N=17 -14.41 (12.98)	N=11 -10.73 (11.38)	0.3192	N=26 -17.73 (14.49)	N=20 -12.10 (12.38)	0.132
2 knee only	N=51 -16.98 (17.48)	N=47 -9.64 (13.82)	0.0113	N=72 -20.13 (14.92)	N=72 -14.96 (14.41)	0.0484
Both	N=17 -15.12 (13.67)	N=12 -9.83 (14.12)	0.3887	N=21 -13.29 (14.22)	N=14 -15.50 (7.45)	0.5769
Total	N=85 -16.09 (15.97)	N=70 -9.84 (13.34)	0.0029	N=119 -18.39 (14.65)	N=106 -14.49 (13.28)	0.0425

1 Results from FDA statistical review (Suktae Choi). P-values are from ANCOVA with factors of baseline and treatment groups as specified in the study protocols. Number of patients refers to those in the completers population as defined by FDA re-interpretation of Sponsor's data (see Tables 3).

Table 19 summarizes the efficacy results for patient global for study 109 and 109-US as determined by the FDA statistician based upon the assignment of patients into the ITT populations as noted earlier. Here, in contrast to the WOMAC pain and physical function noted above, the 1 knee and 2 knee-treated populations suggest a significant treatment effect in favor of Pennsaid.

Table 19: FDA-Statistical Comparisons (ITT) for Patient Global[1]

	Study RA-CP-109			Study RA-CP-109-US		
	N Mean (std dev)			N Mean (std dev)		
	Penn	DMSO	P-value	Penn	DMSO	P-value
1 knee only	N=23 -1.17 (1.23)	N=18 -0.44 (1.25)	0.007	N=37 -1.24 (0.93)	N=33 -0.73 (1.10)	0.0472
2 knee only	N=63 -1.25 (1.36)	N=75 -0.67 (1.15)	0.0035	N=100 -1.35 (1.28)	N=110 -1.00 (1.16)	0.0393
Both	N=19 -1.21 (1.32)	N=15 -1.33 (0.98)	0.8635	N=24 -1.42 (1.10)	N=19 -1.11 (1.15)	0.3676
Total	N=105 -1.23 (1.31)	N=108 -0.72 (1.17)	0.0003	N=161 -1.34 (1.18)	N=162 -0.96 (1.14)	0.0036

1 Results refer to WOMAC physical function scores from FDA statistical review (Suktae Choi). P-values are from ANCOVA with factors of baseline and treatment groups as specified in the study protocols. Number of patients refers to those in the ITT population as defined by FDA re-interpretation of Sponsor's data (see Tables 4).

Reviewer's comment: *The patient global in these studies, as described earlier, is really another type of efficacy assessment, not an attempt to capture the patient experience with/tolerability to the drug.*

Table 20 summarizes the efficacy results for patient global for study 109 and 109-US as determined by the FDA statistician based upon the assignment of patients into the "completers" populations as noted earlier. Results similar to the ITT population are noted.

Table 20: FDA-Statistical Comparisons (completers) for Patient Global[1]

	Study RA-CP-109			Study RA-CP-109-US		
	N Mean (std dev)			N Mean (std dev)		
	Penn	DMSO	P-value	Penn	DMSO	P-value
1 knee only	N=17 -1.35 (1.32)	N=11 -0.91 (11.38)	0.0101	N=26 -1.50 (0.76)	N=20 -1.00 (1.03)	0.0481
2 knee only	N=51 -1.43 (1.32)	N=47 -0.83 (1.22)	0.0119	N=72 -1.60 (14.92)	N=72 -1.32 (1.14)	0.1951
Both	N=17 -1.35 (1.32)	N=12 -1.08 (0.90)	0.5354	N=21 -1.38 (0.97)	N=14 -1.57 (0.94)	0.5714
Total	N=85 -1.40 (1.30)	N=70 -0.89 (1.19)	0.0009	N=119 -1.54 (1.10)	N=106 -1.29 (1.10)	0.1057

1 Results from FDA statistical review (Suktae Choi). P-values are from ANCOVA with factors of baseline and treatment groups as specified in the study protocols. Number of patients refers to those in the completers population as defined by FDA re-interpretation of Sponsor's data (see Tables 3).

Acetaminophen:

Table 21 displays the amount of rescue acetaminophen 325-mg tablets taken by each patient throughout each study was determined by weight and between group differences examined by Student's t-Test. As analyzed by the Sponsor, there were significant differences (i.e. $p < 0.05$) for the per-protocol population between Pennsaid and DMSO in study 109, but the trends all appear to favor Pennsaid. Although there were no significant differences between patients treated with PENNSAID or DMSO in study 109-US, there were some suggestive trends in the ITT population of greater use than the DMSO group.

Table 21: Analysis of Acetaminophen Use-All Sites[1]

Population	Treatment Group Mean (SD)		P-value
Study 109-US			
	Pennsaid	DMSO	
All patients treated (N = 326)	23.7 (22.6)	24.5 (24.6)	0.7730
ITT-pain (N = 277)	25.6 (23.0)	23.5 (23.8)	0.4729
Per Protocol-Pain (N = 171)	26.9 (24.2)	29.1 (25.4)	0.5580
ITT-function (N = 276)	25.8 (22.9)	23.5 (23.8)	0.4323
Per Protocol-function (N = 171)	26.9(24.2)	29.1 (25.4)	0.5580
ITT-global (N = 275)	25.3 (22.5)	23.5 (23.8)	0.5246
Per Protocol-global (N = 169)	26.5 (23.6)	29.1 (25.4)	0.4988
Study 109			
All patients treated (N = 205)	31.9 (31.3)	38.2 (36.1)	0.1805
ITT-pain (N = 187)	33.0 (31.7)	40.7 (37.0)	0.1266
Per Protocol-Pain (N = 122)	29.8 (29.4)	48.7 (39.2)	**0.0028**[2]
ITT-function (N = 187)	33.8 (31.5)	40.3 (37.0)	0.1921
Per Protocol-function (N = 121)	30.2(29.4)	48.7 (39.2)	**0.0036**[2]
ITT-global (N = 186)	33.7 (31.7)	40.3 (37.0)	0.1900
Per Protocol-global (N = 121)	30.2 (29.4)	48.7 (39.2)	**0.0036**[2]

1. Taken from Table 55 (unpaginated document for RA-CP-109-US) and 43 (stamped page 136, RA-CP-109). These data are number of 325 mg tablets used during the entire study per patient.
2. All comparisons were by Student's t-test.

Reviewer's comment: *This usage of APAP seems surprisingly low for trials of this duration and in this population. An information request (July 8, 2002) was sent to the Sponsor to clarify the use of APAP and other analgesic and/or anti-inflammatory agents (either Rx or OTC) that occurred during these trials. The response (July 19, 2002) was confusing in that the numbers were the same for both treatment groups in study 109 to that listed in the Table 21 above, but for study 109-US* ***the results were dramatically different*** *(no comment was made on this difference by the Sponsor). Rather than Pennsaid = 23.7 mean tablets as noted in Table 21 above, the new number was 70.1; and for DMSO the new number was 68.4 vs. 24.5. According to this July 19 response, the 'average tablets taken per day' for the Pennsaid and DMSO groups in study 109 and 109-US were 0.9, 1.1, 1.2 and 1.3, respectively. An argument for allowing treatment of more than one knee during the trials if symptomatic was to lessen the need for rescue acetaminophen. Unfortunately, this issue was not addressed directly by the Sponsor and can not be answered with the information submitted since treatment arms (i.e. one, two or both) are not listed for comparison. However, the data above suggests that use of Pennsaid on both knees did not decrease the use of rescue acetaminophen.*

In addition, the July 19 submission noted that there were 20 vs. 23 (Pennsaid vs. DMSO) patients in study 109 who used prophylactic ASA; this compares to 27 vs. 26 in study 109-US. For use of NSAID-type compounds, there was 1 vs. 14 patients in study 109 and 8 vs. 13 in study 109-US. For use of opioid-related drugs, there was 1 vs. 2 in study 109 and 1 vs. 1 in study 109-US.

Covariates:
In study 109-US, analysis revealed no differences ($p < 0.05$) between groups for any of the relevant variables noted earlier as possible 'relevant' covariates to be included in the ANCOVA analysis of the primary outcomes.

Reviewer's comment: *One of these variables included one vs. two knees being treated. This suggests that there were no significant differences between the treatment groups at baseline or end of study in the number of patients that had 1 or 2 knees treated.*

Integrated Summary of Safety

This ISS is not intended to be the only review of the safety of Pennsaid although it does attempt to integrate all relevant safety information; this relates to the nature of the compound and how the review of this NDA was divided. Therefore, the safety review of the this NDA has been addressed as follows and the interested reader should also see these other reviews:

Hon-Sum Ko, M.D.	Dermatologic Review
Tatiana Oussova, M.D.	Overall Safety Review

Reviewer's comment: *This safety review will concentrate on studies 107-96, 109 and 109-US.*

Safety data were obtained in three ways.

1. At each visit (telephone or clinic) the coordinator questioned the patient in an open-ended fashion about any adverse events (AE) by asking the following question: "Since the last visit, did you experience any", followed by a checklist (yes/no) of AEs commonly reported with oral diclofenac (the checklist and AEs related to oral diclofenac were not mentioned in protocol 109). For any significant events, reported in telephone visits, the investigator asked the patient to come into the clinic for a confirmatory visit. **Significant events included redness with edema, vesicle or blister formation at the application site, wheezing, hives or similar allergic systemic reaction, GI bleeding, etc.** At the confirmatory clinic visit, the investigator documented all of the details of the AE on the CRF.
2. At each clinic visit (1C, 6C and 12C/Final) the coordinator assessed the application site for signs of irritation by the study lotion, **using the grading scale** found in the CFR as follows:

   Examine of application site (s) for signs of irritation and their score:

   (a) No visible reaction or equivocal response (questionable reaction), **score (0)**
   (b) Dryness or flaking, **score (0.5)**
   (c) Erythema (redness), **score (1)**
   (d) Erythema with induration (i.e. swelling), **score (2)**
   (e) Erythema with induration and vesiculation (i.e. small blisters £ 5 mm), **score (3)**
   (f) Erythema with induration and bullae (i.e. large blisters > 5 mm), **score (4)**

   If a patient developed skin irritation that was evaluated at a score of >2, the investigator discontinued treatment and completed the appropriate AE and patient withdrawal.

3. At each clinic visit (1C, 6C and 12C/Final) the coordinator asked questions (to which the patient answered yes or not) **in a direct fashion** from a checklist of the following adverse effects:

   New heart burn
   New epigastric pain
   Bloating or dyspepsia
   Melena
   Hematemasis
   New wheeziness
   Facial swelling
   Urticaria
   New Bruising

Adverse events (AE) were coded using a COSTART dictionary and tabulated by as to categories such as frequency, severity, and outcome. Any abnormality recorded in response to the checklist questions or standard grading scale for irritation was recorded as an AE on the appropriate CRF. For **any serious AE** the investigator promptly notified Dimethaid Health Care Ltd. and the principal investigator's Ethics Review Board or Independent Ethics Committee (ERB/IEC).

After recording this information, the investigating physician decided whether or not it was safe for the patient to remain in the trial and recorded this decision on the case report form (CRF). If the physician removed the patient from the trial, a Dropout CRF was completed. On this form, the investigator recorded the date that administration of the product was stopped and the reason for dropping the patient out of the study. **An event was not considered related to application of the lotion if the event occurred in a similar number of patients in each treatment group. Events considered to be related to application of study lotion included events that occurred at the site of application and events related to the characteristic garlic odor associated with the use of DMSO.**

> ***Reviewer's comment:*** *The Sponsor notes this adverse event checklist includes 'common adverse effects of oral NSAIDs'. Serious adverse events are not defined in protocols. According to the sponsor, 'All effectiveness and safety assessment methods used were standard methods [Altman et al. (Steering Committee) 1996; Bellamy et al., 1997].*

In study 109-US only, the **first forty patients** to be randomized were required to provide blood samples, at baseline (Visit B) and at Visit 12C/Final, for **analysis of levels of diclofenac sodium in plasma and DMSO and metabolites of DMSO** (dimethyl sulfide and dimethylsulfone) in whole blood. Diclofenac was measured via a HPLC, with the minimum level of quantitation being 50 ng/mL of plasma. DMSO and its metabolites were measured using a gas chromatography method, with the minimum level of quantitation being 200 ng/mL of whole blood. **As intake of oral diclofenac sodium was prohibited throughout the study,** final blood levels of diclofenac were expected to relate directly to absorption of diclofenac from PENNSAID. On the other hand, blood levels of DMSO and its metabolites were expected to relate directly to use of PENNSAID or the DMSO-control lotion. No specific instructions were given for the sampling with regard to ingestion of food, posture, alcohol, caffeine, nicotine etc.

> ***Reviewer's comment:*** *The sponsored noted in the protocols 'that no relationship is to be drawn between blood levels of any of these substances and efficacy results. However, it was expected (from wording in both protocols) that the low blood levels would explain the absence of typical oral diclofenac-related adverse effects on the gastrointestinal tract. The argument that the Sponsor appears to be making is that blood levels of diclofenac, or any NSAID, predict efficacy and safety (in an unfavorable fashion) for oral agents, but blood levels of diclofenac only predict safety (in a favorable fashion) for topical agents.*

The actual results from trial 109-US (see PK review for details) is that blood levels of either diclofenac or DMSO (and metabolites) was, at steady state, less than the detectable limit of the assay systems. It is not clear from the data submitted, whether these patients had more than one knee treated. Although this will be clarified by an information request to the Sponsor, it can be assumed (based upon the fact that 66% of patients in this trial did so) that at least one patient treated both the target and non-target knee for the study.

Safety Results:

Duration/Degree of Exposure:

Table 22 estimates the exposure to the components of Pennsaid, or control DMSO, for a single patient based upon a single dose, single day, or daily usage if the target alone, or the target and non-target knees were treated for 4-12 weeks.

Table22: Exposures with Pennsaid Use[1]

	Milligrams						
Compound	Single-dose	Day		Completer in study			
				107-96 (28-day)		CP-109-US (84-day)	
		1 knee	2 knees	1 knee	2 knees	1 knee	2 knees
Diclofenac	15	60	120	1680	3360	5040	10,080
DMSO	450	1800	3600	50,400	100,800	151,200	302,400
Propylene Glycol							
Ethanol							
Glycerine							

b(4)

1. Numbers are based on the composition of Pennsaid as noted above. For example, Pennsaid consists of 45.5%(w/w) DMSO, therefore, each 1 mL (this was the dose used 4 times daily for each knee) of Pennsaid delivers 450 mg of DMSO per application. 454, 000 mg = 1 pound.

***Reviewer's comment:** According to the sponsor, the low levels of diclofenac from PENNSAID treatment group noted earlier, accounted for the fact that patients experienced fewer adverse events than would be expected with the use of oral diclofenac. Furthermore, according to the Sponsor it was "understood, from basic principles and/or previous data, that the other ingredients [besides diclofenac] in the carrier [DMSO] lotion had no significant therapeutic effect on the underlying disease" (Section 9.2, Study RA-CP-109, stamped page 50).*

The number of patients and the duration of exposure to Pennsaid in NDA 20-947 are summarized in **Table 23.** As can be seen, most (i.e. 292/441 = 66%) of the controlled data is of short (i.e. ≤ 42 days)duration.

Table 23: Duration of Exposure-Pennsaid Treated Patients (NDA 20-947)

Controlled studies			
Study	**≤ 42 days**	**≤ 99 days**	**Total**
102-93-1[1]	41	0	41
107-96[1]	84	0	84
108-97[1]	50	0	50
109[3]	89	17	106[5]
109-US[4,6]	28	132	160[5]
Total	292	149	441

Open-label studies (months)[2]						
	≤ 1	**≤ 3**	**≤ 6**	**≤ 12**	**> 12**	
EDR	220	14	8	2	0	244
105-95	1364	431	254	217	388	2654
Total	1584	445	262	219	388	2898

1. Exposures are based on study design as per Table 1.
2. Both open-label studies of Pennsaid used on differing joints (small, medium, large) with 20-40 drops, QID. From Table 3, stamped page 249, vol. 1, NDA 20-947.
3. Table 52, page 153 stamped version, RA-CP-109.
4. Table 64, unpaginated PDF version, RA-CP-109-US.
5. These numbers differ from the ITT populations as noted in Table 1, i.e. 105 and 161, respectively.
6. In study 109-US, 51% of patients were < 65 years and 29% were males.

Clinical Laboratory Tests/Vital Signs:
In study 107-96, no clinical laboratory change was viewed as serious. Analysis revealed significant differences (p = 0.031) between treatment groups in the number of patients **with the ALT elevations (≤ 3X ULN).** The numbers of patients were as follows:

- 45% DMSO (4 patients = 4/56 = 7%)
- PENNSAID (1 patient = 1/56 = 2%)
- 4.5% DMSO (0 patients)

Clinical laboratory data were not collected in study 109 or 109-US.

> ***Reviewer's comment:*** *More extensive review of the clinical laboratory findings are available in Dr. Oussova's review. It is important to note that the data that is provided suggests the possibility of significant hepatic and hematologic toxicity associated with DMSO. It should also be noted that at no time was the requirement to demonstrate that Pennsaid is safe with regards to laboratory assessment ever waived.*

In study 109, of the vital signs that were monitored (i.e. systolic and diastolic blood pressure, pulse and respiratory rate. There was a statistically significant difference (p = 0.0308) in study 109-US in pulse rate of –1.1 beats/minute for Pennsaid (mean: final = 73.6 – baseline = 74.5) compared to a +1.4 beats/minute for DMSO (mean: final = 73.4-

baseline = 71.7); the clinical significance of this change seems to be negligible. There were no differences noted in vital sign values for study 109-US.

Adverse Events:

Table 24 lists the incidence of adverse events ≥ 2% (in any treatment group) for study 107-96, 109 and 109-US.

Table 24: Adverse events ≥ 2% in Study 107-96, 109 or 109-US-NDA 20-947[1]

Event	Study 107-96			Study 109		Study 109-US	
	Pennsaid	DMSO 45%	DMSO 4.5%	Pennsaid	DMSO 45%	Pennsaid	DMSO 45%
Total N	**84**	**80**	**84**	**107**	**109**	**164**	**162**
Abdominal pain	2.4	1.3	5.6	3.7	0.9	2.4	0.6
Asthenia	5.6	5.0	3.6	NA	0.9	0.6	0.6
Back pain	5.6	5.0	7.1	0.9	1.8	2.4	2.5
Body Odor	2.4	0	0	NA	NA	0.6	0.6
Chest pain	0	0	2.4	NA	NA	NA	NA
Halitosis	4.8	1.3	0	1.9	NA	0	0.6
Headache	14.3	17.5	13.1	7.5	10.1	8.5	8.0
Infection	3.6	1.3	2.4	0.9	NA	1.8	0
Pain	3.6	7.5	7.1	1.9	NA	6.7	1.9
Diarrhea	1.2	2.5	3.6	0.9	NA	0	1.2
Dyspepsia	7.1	5.0	6.0	3.7	0.9	5.5	4.3
Nausea	0	5.0	1.2	0.9	1.8	1.8	NA
Peripheral edema	2.4	2.5	0	NA	NA	1.2	0
Arthralgia	**34.5**	**40.0**	**29.8**	**1.9**	**4.6**	**3.7**	**1.9**
Arthrosis	8.3	0	0	0.9	0.9	0	1.2
Joint Disorder	**14.3**	**17.5**	**19.1**	**NA**	**NA**	**0**	**NA**
Dizziness	2.4	2.5	1.2	0.9	1.8	1.2	0
Paresthesia (at site)	**14.3**	**22.5**	**5.6**	**1.9**	**1.8**	**1.8**	**3.1**
Cough increased	2.4	2.5	2.4	2.8	1.8	1.2	0.6
Pharyngitis	3.4	2.5	9.5	2.8	3.7	4.3	1.2
Dry skin (at site)	**35.7**	**13.8**	**1.2**	**38.3**	**21.1**	**40.9**	**29.6**
Pruritis (at site)	**10.7**	**7.5**	**3.6**	**0**	**1.8**	**0.6**	**0**
Rash (at site)	**13.1**	**7.5**	**3.6**	**1.9**	**3.7**	**11.0**	**3.7**
Taste perversion	**4.8**	**3.8**	**4.8**	**3.7**	**1.8**	**1.8**	**2.4**

1 From Tables 82 (study 107-96), Table 69, 70, 72 (study 109) and Table 79, 80, 82 (study 109-US). Results are summarized in this table without regard to relatedness or severity. NA = not available.

Reviewer's comment: *It is of note the sometimes widely differing event rates across these three trials. In this regard,* ***arthralgia, joint disorder and paresthesia seem to jump out*** *and there seems to be a trend of lower event rates in those trials that had more patients exposed for a longer period of time; the opposite in usually true. Also, many events are listed as NA, but it is unclear from the data if these represented "0" or the data were not available (i.e. apparently not collected).*

For purposes of understanding the adverse event rate and profile of Pennsaid in studies 107-96, 109 and 109-US, one must assume that events for the Pennsaid and

DMSO 45% treatment arms may be related to DMSO. If this is the case, then none of the safety data in study 109 or 109-US has any true control treatment arm with which to compare event rates.

Adverse Events Causing Withdrawal/Serious Adverse Events:

Adverse events (listed as either "serious" or "significant") in studies 107-96, 109 or 109-US are listed in **Table 25.** For study **109-US,** Table 141 and 142 list 16 events under these categories; 7 patients treated with Pennsaid and 2 patients treated with DMSO withdrew due to these events. In **study 109**, the Sponsor notes that 18 patients withdrew (9 in both treatment groups, see *Reviewer's comment* below) due to adverse events. In **study 107-96** 19 patients withdrew (8 Pennsaid, 5 Control DMSO 45%, 6 placebo-DMSO 4.5%).

Table 25: Adverse events (serious or significant) in Study 107-96, 109 or 109-US[1]

Event Term	Study 107-96			109		109-US	
	Pennsaid	DMSO 45%	DMSO 4.5%	Pennsaid	DMSO 45%	Pennsaid	DMSO 45%
Total N	**84**	**80**	**84**	**107**	**109**	**164**	**162**
Aphasia[5]	1						
Arrhythmia[5]							
Chest pain/angina					1[4]	2	2[2]
Edema		1			1		1
Halitosis	1						1
Rash	2		1	2	1	2	
Dry skin (knees)						1	
Asthma					1		1
Melena							2[3]
Dizziness					1	1	
Headache				6	6	1	1
Paresthesia		1			3	1	
Accidental injury				1[4]	1		
Cerebral ischemia					1		
Dyspepsia				3	1		
Flu syndrome				1			
Vertigo					1		
Epistaxis					1		
Kidney pain					1		
Migraine				1			
Rhinitis				1	2		
Hernia				1			
Infection				1			
Sleep disorder				1			
Acne				1			
PSA increase				1			
Arthralgia	1	2	3	1	3		
Back pain			2		1		
PT increased					1		
Contact dermatitis				1			
Urinary frequency					1		
Pharyngitis/bronchitis			1	1	3		
Vaginitis					1		

Abdominal pain				1			
Pruritis	1	1		1			
Gastritis				1			
Periodontal abcess					1		
Asthenia	1						
Total	**7**	**5**	**7**	**26**	**33**	**8**	**8**

1 From Tables 311, 312 (study 107-96, section 14.3.2), Table 481, 482 (study 109, section 14.3.2) and Table 141, 142 (study 109-US, section 14.3.2).

2 Pt 39002 (DMSO) was treated for 8 days and developed chest pain on 2/23/01; he had bypass surgery on 2/26/01. The patient was listed as taking NO concomitant medications and yet this was felt to be "Not Related" to study drug.

3 Two patients were applying DMSO, one was only taking guaifenesin while the other was taking a variety of medications included ASA and Celebrex. The Sponsor interpreted this data "possibly" related to study lotion but not that "these adverse events are common to oral NSAIDs".

4 These were the two patients listed as "serious" in study 109-US, both were withdrawn.

5 These two events were listed as "serious" in study 107-96; the patient (patient 1032, 74 y/o female) that had aphasia due to a CVA was discontinued from the study; patient 4023 who developed an arrhythmia was a 66 y/o male.

Reviewer's comment: *In* ***study 109-US,*** *three events are listed as "chest pain", however, these events are not listed in the adverse events noted above in Table 24. There was one event listed in Sponsor Table 79* ***as "myocardial infarction"*** *in a patient treated with Pennsaid, this case* ***was not listed in the "serious" or "significant" tables*** *(i.e. Table 141 and 142, respectively). In* ***study 109,*** *the Sponsor notes that 18 patients withdrew (9 in both treatment groups) but review of Tables 481 and 482 only suggests that 15 (7 in DMSO, 8 in Pennsaid) withdrew; the other three are probably patients that were described as being in "too much pain" but their treatment assignment is not listed in the table nor described in this section.*

Special Safety Topics-Dermatologic Safety:

In Dr. Ko's "Conclusions" for the dermatologic safety review, it is noted that these safety studies were not conducted under GLP conditions, and the study reports "contain internal inconsistencies".

Reviewer's comment: *Based upon the atypically low number of events (other than those of skin) reported by the Sponsor during these dermatologic safety trials (some of which lasted up to seven weeks), in his 24-page consult, Dr. Ko uses the terms:*

- *discrepancy (twice)*
- *inaccurate*
- *contradictory*
- *caution should be used in interpreting this data*
- *not consistent(twice)*
- *confusing (twice)*
- *conflicting, must be error*
- ***possibility of underreporting of adverse events*** *(three times, pages 8, 11 and 15 for studies 100-89, 101-89-2 and 104-93-3).*

*A conclusion from Dr. Ko's review is that "**Adverse event reporting in these studies appears to be inadequate**".*

Since trial 107-96 (28-day, knee study) had Pennsaid with both high (45%) and low (4.5%) DMSO controls, adverse events (related or not to the use of study lotion) at the site of application that occurred during this study are noted in **Table 26.**

Table 26: Adverse events (%) associated with Pennsaid and Controls: Study 107-96

Application site event	Pennsaid (N = 84)	45% DMSO (N = 80)	4.4% DMSO (N = 84)
Vasodilation	0	1.3	0
Paresthesia	14.3	22.5	5.6
Dry skin (desquamation)	36	14	1
Pruritis	11	8	4
Rash	13	8	4

Reviewer's comment: It is interesting to note the high percentage of patients that noted paresthesia (especially for 45% DMSO) and "dry skin" (desquamation, described as peeling, scaling and flaking) especially for the Pennsaid. These data suggest that Pennsaid and DMSO, especially since DMSO is an integral part of Pennsaid, have similar toxicities and should be considered that way when evaluating the safety profile in the pivotal studies. It also may suggest a mechanism of action (i.e. paresthesia) for the DMSO. It is of interest to also note that 2.4% of patients applying Pennsaid complained of 'body odor' and 4.8% of patients also complained of 'halitosis' and 'taste perversion' (for each event). For details of the dermatologic safety results, those interested should read the consult by Dr. Hon-Sum Ko, (May 16, 2002).

Deaths:

There was one death during the controlled clinical trials in NDA 20-947. This was subject 103 (101-89-2, 45 year old, Caucasian male) due to cancer.

***Reviewer's comment:** The CRF contains no details on the cancer or death. In fact, the CFR is not consistent about this patient since in one place the reason for withdrawal is noted to be for a "personal reason" whereas in other areas it is noted, "Patient contracted cancer and could not continue, died."*

Safety Updates:

There have been no updates on safety since the end of study109-US on May 18, 2001.

***Reviewer's comment:** In the July 19, 2002 response to the Division's request for information to the question "When was the last patient treated with Pennsaid?" the Sponsor confirmed that this was May 18, 2001; it was July 27, 2000 for study 105-95 (open-label study). No other safety updates have been received.*

Efficacy Discussion/Conclusions

The aim and requirement of efficacy studies for topical therapy of OA of the target knee requires statistical superiority of all three co-primary endpoints (pain, function and patient global) compared to a control group.

Upon careful review of the data included in this NDA, it became clear that the intended "compassionate use" of Pennsaid to the "non target" but symptomatic knee of the patients in studies 109 and 109-US was extensive. In fact (see Table 7), only 18% in study 109, and 22% of patients in study 109-US, had only the "target" (i.e. where efficacy was evaluated) knee treated during the entire study. The remainder (82% in study 109 and 78% in study 109-US) had the non-target knee treated for all (i.e. "2 knee only") or a portion (i.e. the "both knees") of the study. This obscures the ability to assess the benefit of therapy of a single knee. Without a pre-specified stratification strategy, the number of patients in these three treatments groups were unbalanced and under-powered which limits the robustness and accuracy and any conclusions regarding efficacy.

In conjunction with the statistical reviewer (Dr. Suktae Choi), the data were reanalyzed by separating the population in three categories:

- target knee only treated during the entire trial (i.e. 1 knee only group)
- target and non-target knee treated during the entire trial (i.e. 2 knees only group)
- target knee treated during all the trial, non-target knee only during part of the trial (i.e. both knees group)

From this reanalysis, it can not be concluded from the data that Pennsaid is an effective treatment for OA of the target knee. WOMAC pain (Tables 15 and 16) and WOMAC function (Tables 17 and 18) were not significantly different between Pennsaid and DMSO for the patients (ITT or completers) who had only the target knee treated (the "1 knee only" group); the same conclusion applies for the target knee of patients that also had the non-target knee treated for a portion of the study (i.e. "both knees" group). There was a difference between Pennsaid and DMSO for the patient global endpoint, but this difference was only seen in the "1 knee" treated group of patients (Tables 19 and 20).

On the other hand, **when both the target and the non-target knee were treated for the entire study (i.e. "2 knees") with Pennsaid, it did demonstrate consistent statistical superiority to DMSO with all three endpoints; however, only the target knee was studied for efficacy, not the other non-target knee.** These results, where treatment of the target and non-target knee suggests efficacy of Pennsaid at the target knee, may represent a "double-dosing" effect.

It is noteworthy that the data also do not support the reason offered by the Sponsor for this "compassionate use", since the amount of rescue acetaminophen taken by patients did not seem to differ significantly between the Pennsaid and DMSO-treated arms.

However, the "2-knee" results, as discussed above, are suggestive that Pennsaid may be efficacious at the target knee. If this is true, how does Pennsaid "work" if the diclofenac (in blood and synovial fluid) and the DMSO levels (in blood) associated with Pennsaid use are below the level of detection for patients; even for patients who are supposedly at steady state? Does this mean that there might be some systemic component of Pennsaid that was not analyzed but that is related to the dose administered such that a "double dose" of treatment to both the target and non-target knee resulted in efficacy as measured at the target knee? Or does this mean that maybe the wrong samples were being analyzed? It is worth noting that in the Medical Officer review for RIMSO-50 (NDA-788; December 1, 1977) which is 50% DMSO instilled into the bladder, that during phase one studies (2 patients) a single instillation of 50 ml of 50% DMSO into the bladder (voided after 30 minutes) resulted in peak serum concentrations of DMSO after 4-6 hours. The label for Kemsol (70% DMSO, see below) also notes that detectable levels of DMSO can be detected 5 minutes after skin application. In the RIMSO-50 NDA, however, both the unchanged drug and DMSO metabolite (dimethyl sulfone) were isolated from urine. Dimethyl sulfone appeared in the serum after about 48 hours and persisted for 370-380 in these two subjects. These studies support the statement in the RIMSO-50 product monograph (prepared, May 5, 1980) that topical DMSO is absorbed and generally distributed in the tissues and body fluids. There is at present, no explanation for the apparently different PK results for DMSO in this NDA, but perhaps urine also needs to be analyzed.

Another possibility for failure to demonstrate consistent efficacy of Pennsaid from the DMSO control may be that DMSO is itself an active agent and the diclofenac component is not sufficient to add significant or consistent enough additional efficacy to the Pennsaid solution? This possibility is suggested in the *Drugs Facts* labeling noted above, is also suggested by the literature, and is somewhat supported by information in this NDA. For example, in study 102-93-1, Pennsaid appears to be efficacious against a placebo that had 4.5% DMSO, but not against one with 45% DMSO.

Further study will be necessary to address these questions but it may be possible that at least some of the effect of DMSO relates to an anesthetic, rather than anti-inflammatory mechanism. Studies in the literature (Neurosci. Lett., Feb 19, 1993; 150[2]: 145-8) note that DMSO, applied to cat sural nerves, blocked conduction in these C fibers (felt to mediate pain sensation). This blockage, which was almost immediate with 15% DMSO and higher, was suggested as a possible mechanism for the analgesic effects of DMSO.. Future study should also address the issue of dose and dosing interval since no such studies have been conducted to date.

Safety Discussion/Conclusion:

If it is true that "absence of evidence is not evidence of absence", then **the data submitted in NDA 20-947 do not allow the conclusion that use of Pennsaid is sufficiently safe.** As noted earlier, the **Sponsor decided to forgo testing of any clinical laboratory tests in either study 109 and 109-US.** Therefore, the clinical laboratory safety of Pennsaid was not established in the two trials that contained the largest and longest exposure to Pennsaid (see Table 23). It is only during careful monitoring of these important clinical parameters during IND studies that such adverse can be detected. Based upon the information available for DMSO alone, as noted earlier in this review, there is ample reason to monitor patients during these studies. In fact, the recommendation in the *Drug Facts* label for DMSO that **liver and renal function tests and complete blood counts be monitored while on therapy** appears to be good advice since **similar concerns have been noted on review of the rest of the safety data in this NDA** (see Dr. Oussova's review for details).

The sense of under-reporting of adverse events as noted above from Dr. Ko's conclusions in his review of the dermatologic safety studies is of concern. He notes that "**Adverse event reporting in these studies appears to be inadequate**" and in the comments section on three of the five trials submitted he comments "It is unusual that there were no adverse events other than skin test reactions in a study of 27 subjects [study 104-93-3] lasting for almost 7 weeks. **There is a possibility of under-reporting".** There is also concern about the notable differences in adverse reporting events between trials (see Table 24) and the seeming lack of detail to even such important adverse events as death and myocardial infarction as discussed above. The fact that no safety update has been submitted to the NDA is of even more concern as to whether an accurate assessment of the safety of Pennsaid has been completed to date.

> *Reviewer's comment: A teleconference was held (July 26, 2002) between the Division and the United Kingdom's Medicines Control Agency. At this conference, it was noted that since launch of Pennsaid in England (March 26, 2001) and the last update (December 31, 2001), approximately 7,900 patients (duration unknown) have been exposed to Pennsaid. However, during this time period, there were "precisely zero adverse events". This also appears to say something about efficacy too.*

Why is it important to be so concerned about establishing the safety of Pennsaid? As noted above, there may be two active components to Pennsaid as regards efficacy. The adverse events associated with diclofenac use are well known. The adverse events associated with DMSO use have also been noted earlier in this review. But it is the magnitude of exposure to all the ingredients of Pennsaid that is of most concern. Estimates (see Table 22) are 5-10 grams of diclofenac and 150-300 grams of DMSO when the target, or the target and non-target knees, respectively, are treated for the duration of study 109-US. The amount of diclofenac for "2 knees" actually compares to a range of those approved for oral formulations of diclofenac i.e. 8.4 grams (100 mg daily) to 16.8 grams (200 mg daily).

The potential to be exposed to kilogram range amounts of **DMSO** when used chronically is of concern. In the labeling for KEMSOL (70% DMSO, a topical agent approved in Canada for scleroderma, prepared May 28, 1976) it is "**contraindicated** for use in patients with known eye disease, renal or liver dysfunction, and in patients with a history of allergy or skin sensitivity to DMSO". Furthermore, "application of Kemsol to mucous membranes is not advisable". Under **warnings** it is noted that "Kemsol applied to already infected skin may induce invasion by certain microorganisms" and that it may cause "mild sedation and drowsiness". This label also notes "Proteinuria was observed in a number of patients treated topically with Kemsol and one of these subsequently died from **renal failure**". The KEMSO label also notes "**ketonuria, bilirubinemia**, and increased alkaline phosphatase" can occur.

But there may be even more components that may contribute to potential safety concerns. **Propylene glycol** (PG) is an important constituent of Pennsaid. PG is present in many pharmaceutical products, lotions, ointments and cosmetics, as well as being a major constituent of coolants and airplane de-icers. Although considered as GRAS by FDA, serious adverse effects have been seen. PG is metabolized in the body to pyruvate and lactate. **Central nervous system depression** and severe **metabolic acidosis with hyperosmolality** occurred in a child who, it was later discovered, did not significantly metabolize PG and so the acidosis resulted from increased concentrations of lactate and pyruvate. Although usually of minor clinical importance, hyperlactemia is usually seen in patients with renal insufficiency. **Cardiorespiratory arrest** occurred in another infant and seizures and respiratory depression have also occurred in children who have ingested medications containing PG. Hyperosmolality related to topical PG occurred in 9 of 262 hospitalized burn patients and 4.5% of 487 patients with eczematous contact dermatitis **developed localized dermatitis** from application of PG when used as a vehicle. In some studies, PG is considered a strong allergen. Of note, there has also been a report of **acute renal failure** in a previously healthy 16 year-old who received large doses of pentobarbital and phenobarbital given to control his new onset of seizures. It was later discovered that these medications contain PG (estimates of 300-700 mg/mL) which is in the range for the concentration of PG in Pennsaid [redacted] There has also been a case of PG intoxication in a 58 year-old schizophrenic man with renal disease. It was speculated that in this case PG probably accumulated because of impaired renal clearance secondary to renal disease.

b(4)

Once again, **the lack of information on concomitant use of Pennsaid and other medications likely to be used in patients with OA, such as NSAIDs is of concern** and does not allow any conclusions as to whether Pennsaid use in this situation is likely to be safe. In fact, the literature experience with Pennsaid and sulindac and the development of a peripheral neuropathy and segmental demyelination (noted earlier in the review) would suggest there is reason for concern. It is unclear what role kidney function (or lack thereof) may play with regards to altering the adverse event profile of the components of Pennsaid, although it does contain diclofenac which carries with it the known risks of NSAIDs. Furthermore, the potential for interactions between Pennsaid and intra-articular therapies commonly used in OA of the knee also needs to be considered since such use would likely happen.

Overall, the lack of information on certain aspects of the safety of Pennsaid, combined with the concern of under-reporting of adverse events, does not support the conclusion that long-term use of Pennsaid is safe.

"Risk'Benefit" Analysis/Overall Conclusions

The conclusions that can be draw regarding the efficacy and safety of Pennsaid are as follows:

1. There is insufficient evidence to suggest that Pennsaid in effective in the treatment of OA of the knee. Data generated with patients who had Pennsaid treatment to two knees (i.e. the target and non-target knee) does not allow the conclusion that treatment to one or two knees is effective to each of these knees. This is a necessary conclusion for a topically applied NSAID.
2. Evidence in the NDA suggests that DMSO is an active ingredient of Pennsaid. It is noted in the labeling for RIMSO-50 and Kemsol that DMSO can have several effects, including against inflammation, but the mechanism for this observation is unknown.
3. The evidence in this NDA suggests that Pennsaid is not effective for treatment of _____
4. There is no evidence to suggest Pennsaid is effective, as there is with oral NSAIDs (including diclofenac) at _____ b(4)
5. There are significant gaps in the assessment of the safety of Pennsaid. This is particularly true for clinical laboratory assessments. These gaps could be clinically meaningful and could relate to the effects of one, or more than one, component in the Pennsaid lotion formulation (especially DMSO). In future studies with Pennsaid, it is critical to monitor liver and renal functions (including analysis of urine) and complete blood cell counts at a minimum along with consideration of complete ophthalmologic examinations.
6. Since the majority of patients/subjects studied in this NDA were Caucasian 68% in dermatologic studies) it is unclear how the safety and efficacy data in this NDA will generalize to a more diverse population if approved.
7. It is unclear from the dermal safety studies if they were conducted with the "to be marketed" formulation. Solubility of the ingredients between formulations used in clinical study vs. that marketed may affect safety (and efficacy), hence it is unclear how these studies allow accurate conclusions regarding the safety of Pennsaid. In addition, the dermal safety studies were not conducted under GLP conditions.
8. DMSO is a skin irritant; this irritancy is enhanced by diclofenac.
9. Adverse event reporting appears to be inadequate in the dermatologic safety studies.

10. There is no information on co-use with oral NSAIDs or COX-2 agents. It is highly likely that this will occur if Pennsaid is made available. This may even be more likely if it is accepted (and written in the label) that the mechanism of action of Pennsaid does not involve similar mechanisms of oral NSAIDs.

> ***Reviewer's comment:*** *Assuming that efficacy at a single knee, or both knees if so treated, can be concluded, this benefit will need to be weighed against the likelihood (even if there are absolutely no other adverse events associated with its use) that the patient will also experience a rash, itching, desquamation and paresthesia at the application site, but also body odor, taste perversion and halitosis. It is highly likely that patients will seek to minimize these events by use of oral agents including acetaminophen, NSAIDs (both prescription and OTC) and COX-2agents along with occasional injection of the knee with steroids and viscosupplements. These, and many other issues, need to be factored into future studies with Pennsaid. It is of interest to note, in an article entitled, " Medical use of dimethyl sulfoxide (DMSO)", (Rev. Clin. Basic Pharm. Jan-June, 5 (1-2), 1-33: 1985) that the author notes "Final approval of topical DMSO for treatment of rheumatic diseases in particular will require a multi-center, randomized comparison between high and low concentrations of DMSO and an orally-active, non-steroidal anti-inflammatory agent". If Pennsaid is substituted for DMSO, this sounds like timely advice.*

Regulatory Discussion

The Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products has no current (or former) guidance documents that relate to topical analgesics. Lacking such guidance, during the IND phase of drug development Sponsors (of all topical agents) have been encouraged, as with Dimethaid International for Pennsaid, to follow the guidance for development of drugs intended for use in OA. The efficacy of topical NSAIDs or analgesics for OA, in contrast to oral NSAIDs and analgesics, is not firmly established. Therefore, an important regulatory goal is the establishment of robust data regarding efficacy. Importantly, safety can not be assumed, it too must be demonstrated and not extrapolated from what may be incomplete or conflicting data. And in contrast to oral NSAIDs, efficacy needs to be established at every joint a topical agent is applied if the effect is (as is argued) local and not systemic.

Therefore, **Pennsaid is not approvable at this time.** Data provided in this NDA are not sufficient to conclude that Pennsaid treatment for OA of the knee is effective, and safe. It is important that every effort be made to adequately characterize the safety profile of a therapy to allow a risk-benefit assessment especially since the data in this NDA suggest that patients will tend to want to use this topical on a longer-term basis. Since Pennsaid may well be a drug delivery system that potentially exposes patients to amounts of three potentially active drugs (diclofenac, DMSO, and propylene glycol), from a safety

perspective this deserves carefully scrutiny. Were Pennsaid to be approved, so-called "off-label" use would undoubtedly occur due to common perceptions about topical analgesics. The Sponsor has already acknowledged their interest in such use (June, 1995 FDA meeting minutes).

Future data needs to allow the conclusion that Pennsaid is effective if applied to only one OA knee. Furthermore, future studies of Pennsaid need to address safety with concomitant oral NSAIDs and COX-2 agents. Consideration should also be given to studying Pennsaid in patients who experience intra-articular injections (i.e. steroids or viscosupplements) since the knee is a frequent target for these interventions. The design of future trials should also include an oral NSAID and/or COX-2 agent/s. Their inclusion in a trial would allow for more robust comparisons of both efficacy and safety between topically applied, vs. orally-administered NSAIDs.

If further study of Pennsaid demonstrates that it is a safe and effective alternative to existing therapies for OA of the knee, this would be a welcomed addition to the therapeutic armamentarium for this very prevalent disease.

Financial Disclosure

In accordance with 21 CFR part 54, a signed form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) and form 3454 was included with the NDA. There were 17 principal investigators (study 109) with subinvestigators and 40 principle investigators (study 109-US) with subinvestigators listed. Only one principle investigator ———— noted "significant equity interest in Dimethaid" in study 109-US.

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/s/

James Witter
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Lawrence Goldkind
8/1/02 04:37:41 PM
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8/5/02 01:19:55 PM
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Team Leader Memo

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Analgesic and Rheumatic Drug Products

Medical Officer Team Leader Memorandum

Date: December 4, 2006

To: File, NDA 20947

From: Jeffrey Siegel, M.D.
Clinical Team Leader
Division of Anesthetic, Analgesic and Rheumatic Drug Products

Re: NDA 20947 resubmission
PENNSAID ®
topical solution w/w
1.5% diclofenac sodium
Dimethaid International Inc.

1. Background

PENNSAID is a topical solution of the approved non-steroidal anti-inflammatory drug (NSAID) diclofenac sodium 1.5% in 45.5% DMSO. The DMSO component is intended to enhance dermal penetration of the active ingredient, diclofenac sodium. The proposed indication for PENNSAID is treatment of signs and symptoms of primary osteoarthritis (OA) of the knee. The sponsor proposes a dose regimen of PENNSAID of 40 drops to each affected knee 4 times daily. The mechanism of action is presumed to be related to the anti-inflammatory and analgesic effects of delivery of diclofenac sodium to the underlying joint and surrounding tissues.

Currently drug treatments for OA are available in topical, oral and intra-articular forms. The available topical treatments available include capsaicin cream (Zostrix) and topical salycilate (Aspercreme). Oral treatments include a variety of NSAID's, including diclofenac sodium (Voltaren), acetaminophen-based products and analgesics (including opioids). Intra-articular treatments include viscosupplementation with hyaluronic acid (Synvisc and Hyalgan) and intra-articular corticosteroids (Kenalog). There are no topical NSAID products available in the US for treatment of OA. However, a topical product containing diclofenac sodium as its active ingredient is approved and marketed in the US for treatment of actinic keratosis (Solaraze, 3% diclofenac sodium). PENNSAID itself was approved in the United Kingdom and Canada for the treatment of OA in 2000 and 2003, respectively.

A draft OA guidance document describes current FDA thinking regarding the key variables that should be addressed in clinical development programs for OA. The evaluation of new products for OA should assess efficacy based on changes in the key patient outcomes of pain assessment, patient global assessment and physical function. Since OA is a chronic disease, clinical trials for efficacy are expected to be at least 3 months in duration.

PENNSAID has a long regulatory history at the FDA. The complicated presubmission regulatory history of PENNSAID is described in detail in the clinical review by Dr. Larissa Lapteva. Briefly, the original NDA for PENNSAID was submitted in December, 1997. It received a non-approvable letter that cited several chemistry issues and a clinical trial that failed to demonstrate statistical significance. The sponsor resubmitted the NDA in August, 2001 and received another non-approvable letter, dated August 7, 2002, because of several deficiencies concerning the data submitted to support safety and efficacy.

The deficiencies cited in the August, 2002 letter were addressed by conducting an additional pivotal trial, study PEN-03-112 and by conducting additional analyses of pre-existing data. The deficiencies and the manner in which they were addressed by the sponsor are shown in Table 1 (this and all other tables copied from the review by Dr. Larissa Lapteva).

The current submission is a resubmission for PENNSAID, submitted by the sponsor on June 28, 2006.

Table 1: Clinical deficiencies indicated in the NA letter from 08/07/2002, and the actions undertaken by the Sponsor to address these deficiencies.

Deficiency	Sponsor's response
1. Demonstration of efficacy at the site of application. Treatment of both the study knee and the contra-lateral knee was allowed in the pivotal studies (RA-CP-109 and RA-CP-109US), while randomization process randomized subjects and not knees	In the new pivotal study (#PEN-03-112) patients were allowed to treat the study knee only; stratification by knee involvement (1 or 2) was done prior to randomization Additionally, the results of study RA-CP-109US were reanalyzed using the data from the study knee only
2. ITT (intent-to-treat) population was inappropriately defined	ITT population was appropriately defined, and the primary analysis of study PEN-03-112 was based on the correct ITT population. Results of studies (RA-CP-109, and RA-CP-109US and 107-96) were reanalyzed on their respective, correctly defined, ITT populations.
3. The main results of the pivotal studies (RA-CP-109 and RA-CP-109US) varied depending on the methods of imputation of missing data	Appropriately conservative, BOCF, method of imputation was used in studies PEN-03-112, RA-CP-109US and RA-CP-109 to support the results of primary analyses
4. DMSO that is viewed by the Sponsor as an inactive ingredient may contribute to the efficacy of PENNSAID®. No adequate demonstration of the adverse event profile of 45.5% DMSO vs PENNSAID® was submitted	The newly designed study PEN-03-112 included an arm containing topical formulation of 45.5% DMSO and no diclofenac sodium, thus allowing evaluation of safety and efficacy of 45.5% DMSO in the placebo- and PENNSAID®-controlled conditions
5. No scheduled measurements of efficacy were done between the baseline and the final study assessments	Efficacy assessments at the intermediate time points were incorporated in the study PEN-03-112
6. Address safety of co-administered therapies,	The newly designed study PEN-03-112 included

particularly oral NSAIDs	an arm containing a combination of PENNSAID® and oral diclofeanc, thus allowing evaluation of safety of PENNSAID® when co-administered with an oral NSAID
7. Inadequate AE reporting in the long term studies EDR and #105-95. Lack of credible long term safety data from a sample size recommended by ICH guidelines (≥300 patients for 6 months, ≥ 100 patients for 12 months)	Study PEN-03-112E was designed and included sufficient amount of patients as well as safety assessments and patient monitoring for up to 12 months
8. No laboratory data were collected in pivotal studies RA-CP-109 and RA-CP-109US	Laboratory data were collected in the newly designed studies PEN-03-112 and PEN-03-112E

2. Review of Efficacy

2.1. Clinical development program

The 19 clinical trials conducted in the clinical development program for PENNSAID are listed in table 4 of the review of Dr. Larissa Lapteva. The sponsor conducted seven phase 3 efficacy trials. However, to assess the evidence for efficacy this review will focus on the results of two phase 3 pivotal trials in patients with knee OA, studies PEN-03-112 and 109-US. The other phase 3 trials cannot be considered adequate trials for efficacy for a variety of reasons, including too short a duration for the chronic condition, knee OA and deficiencies in study design. For details on the additional phase 3 trials, please see the review of Dr. Larissa Lapteva.

2.1.1. Design of Study PEN-03-112

Study PEN-03-112 was a phase 3, 12-week, double-blind, placebo-controlled, 5-arm, multi-center, randomized trial that evaluated efficacy of PENNSAID in patients with knee OA. Patients were enrolled who had primary OA of the study knee with radiographic changes consistent with OA, including joint space narrowing. They were required to have symptomatic, painful OA of the knee requiring the use of an NSAID or other analgesic at least 3 days per week for one month prior to enrollment. They were further required to undergo washout of their previous NSAID or analgesic treatment and to have a moderate flare of knee pain at the baseline assessment using prespecified criteria for the baseline WOMAC pain score. Patients were excluded who had a history of a documented gastroduodenal ulcer or any history of GI bleeding within 6 months of study enrollment, unless there was documented infection with helicobacter pylori that had been treated.

The trial randomized 775 patients to 5 arms as follows:

1. PENNSAID® + oral diclofenac ("combination" arm)
2. PENNSAID® + oral placebo ("PENNSAID®" arm)
3. Vehicle-control solution (45.5% DMSO) + oral placebo ("vehicle control" arm).
4. Placebo solution (2.3% DMSO) + oral placebo ("placebo" arm).
5. Placebo solution + oral diclofenac ("oral diclofenac" arm).

In this trial a low concentration (2.3%) of the vehicle DMSO was used as the placebo treatment to maintain blinding because topical DMSO can cause a characteristic taste. Two controls were included – a vehicle control containing 45.5% DMSO and a placebo control containing 2.3% DMSO – to allow assessment of whether the 45.5% DMSO might itself have clinical activity in relieving symptoms of knee OA. An active control, oral diclofenac, was included that allows a comparison of how topical diclofenac in the form of PENNSAID compares with systemic diclofenac given orally. Finally a combination arm containing both topical PENNSAID and oral diclofenac was included that provides important information concerning the clinical activity and safety of adding oral to topical diclofenac.

In study PEN-03-112, PENNSAID was given at a dose of 40 drops qid to the skin surrounding the knee joint. Oral diclofenac was given as Voltaren XR 100 mg qd. Patients treated only the target knee, regardless of whether they also had symptoms in the contralateral knee. Randomization was stratified based on whether patients had one or both knees affected by OA. Oral NSAIDs, oral glucosamine and chondroitin sulfate, topical capsaicin or methyl salicylate were all prohibited. Patients were allowed to take acetaminophen 325 mg tablets up to four times a day for rescue pain relief throughout the study except for the 3 days prior to the key assessments at weeks 4, 8 and 12.

Study PEN-03-112 had three co-primary outcome variables: changes on the WOMAC (Western Ontario and McMaster Universities) OA Index's dimensions of pain and physical function and change in the Patient Overall Health Assessment Question (POHA). The WOMAC OA index is a validated, well-accepted instrument for the assessment of symptoms of knee OA in clinical trials. The WOMAC pain dimension consists of 5 questions resulting in a 20-point scale. The WOMAC physical function dimension consists of 17 questions resulting in a 68-point scale. The POHA consisted of a single question "Considering all the ways your osteoarthritic (study) knee and its treatment affect you, including both positive and negative effects, how would you rate your overall state of health in the past 48 hours?" with a scale of 0-4.

The statistical analytic plan specified the primary endpoint as the change from baseline to week 12 in the three outcome variables. The primary analysis was a comparison between the PENNSAID group (group 2) and the placebo group (group 4). No adjustment was made for multiple comparisons. The sample size was based on an assumption of mean differences between PENNSAID and placebo of 1.5 (SD 4.5) for pain and 5 (SD 15) for physical function. A sample size of 142 patients/group was calculated to provide 80% power at the 0.05 level using 2-sided testing and an ANCOVA test with baseline score as a covariate. The primary analysis was specified as the intent-to-treat (ITT) population. Missing data were handled using last observation carried forward (LOCF). Baseline observation carried forward (BOCF) was specified as a sensitivity analysis.

2.1.2. Design of Study 109-US

The other key phase 3 trial was study 109-US. The results of study 109-US were submitted to the FDA in a previous NDA submission but the results were not considered adequate because they did not follow ITT principles. The sponsor reanalyzed the data from study 109-US using ITT principles and submitted the new analyses with this submission.

Study 109-US was a phase 3, 12-week, vehicle-controlled, double-blind, randomized, multi-center trial of patients with OA and moderate knee pain comparing topical PENNSAID to topical vehicle control (45.5% DMSO). The dose of PENNSAID was 40 drops 4 times daily applied to the skin surrounding the knee joint. As needed treatment of the contralateral knee with PENNSAID was allowed. Following screening, patients were washed out of prior NSAIDs and analgesics and were enrolled if they had a moderate flare of knee pain based on prespecified levels pain on the WOMAC pain

subscale. Other inclusion and exclusion criteria were similar to those of study PEN-03-112.

The three co-primary endpoints for study 109-US were changes from baseline to week 12 on WOMAC pain and physical function and change in patient global assessment. Using the assumed changes in the primary endpoints, the study had 80% power using a 2-sided test at the 0.05 level of significance and using an ANCOVA analysis with baseline score as a covariate. Missing data were handled as for study PEN-03-112.

2.2. Study conduct

Study PEN-03-112 enrolled approximately 150 patients per study arm. Approximately 68% completed study treatment through 12 weeks with similar proportions in the different study arms. The main reasons for premature discontinuation were adverse events and lack of efficacy. Discontinuations for adverse events were similar in the PENNSAID arm (10%) as with vehicle control or placebo (7% and 11%, respectively). Discontinuations for adverse events were more frequent in the study arms containing oral diclofenac (12% for oral diclofenac and 15% for oral diclofenac/PENNSAID combination). Discontinuations for lack of efficacy were similar in the PENNSAID and placebo and vehicle control arms (approximately 10%) but were lower in the oral diclofenac-containing study arms (3% for oral diclofenac and 6% for oral diclofenac/PENNSAID combination).

Regarding patient demographics for study PEN-03-112, approximately three-quarters of the patients were Caucasian, approximately 6% were Black and approximately 10% were Asian. The mean age was approximately 61 years with approximately 10% over age 75. The demographics were balanced across study arms. The patients enrolled had moderate knee OA with baseline WOMAC pain scores of 13 on the 0-20 scale. Baseline WOMAC pain, physical function and POHA were balanced across study arms.

Study 109-US enrolled approximately 160 patients per study arm. More patients completed 12 weeks of treatment in the PENNSAID arm than the vehicle control arm (38% vs. 33%) with the difference accounted for by a higher rate of discontinuation due to lack of efficacy in the vehicle control arm (26% vs. 17%). More patients discontinued for adverse events in the PENNSAID arm (5% vs. 2%). The population enrolled was approximately 90% Caucasian with the remaining patients primarily Black (approximately 10%). Patient demographics were reasonably well balanced across study arms.

2.3. Efficacy results

Table 2 shows the results of the three co-primary endpoints of study PEN-03-112 as well as the results of the WOMAC stiffness assessment and the patient global assessment. PENNSAID showed statistically significantly greater improvement in the WOMAC pain score, the WOMAC physical function score and the POHA than the placebo control (group 4). Starting with a baseline WOMAC pain score of 13 on the 0-20 scale, there was improvement of 4.7 units with placebo, compared to 6.0 units for PENNSAID. The

group receiving oral diclofenac (group 5) showed improvement of 6.4 units and the combination oral diclofenac/PENNSAID had improvement of 7.0 units. Similar levels of improvement were seen with the WOMAC physical function scores and the POHA.

Table 2: Efficacy analysis across the groups, study PEN-03-112. Mean changes of the scores in five study endpoints after 12 weeks of treatment (ITT, n=772).

Variable	Group 1 PEN+OD N=151	Group 2 PEN+OP N=154	Group 3 VC+OP N=161	Group 4 P+OP N=155	Group 5 P+OD N=151	p-value 2 vs 4	p-value 2 vs 3
WOMAC LK 3.1 pain score ITT population for analysis	N=151(100)	N=154(100)	N=161(100)	N=155(100)	N=151(100)		
WOMAC LK 3.1 pain score Mean change (SD)	-6.95(4.76)	-6.02(4.54)	-4.70 (4.31)	-4.74(4.35)	-6.43(4.11)	0.0150	0.0094
WOMAC LK 3.1 physical function ITT population for analysis	N=150(99)	N=154(100)	N=161(100)	N=153(97)	N=151(100)		
WOMAC LK 3.1 physical function Mean change (SD)	-18.69 (14.03)	-15.75(15.14)	-12.13(14.58)	-12.34(14.72)	-17.48(14.33)	0.0344	0.0255
Patient Overall Health Assessment ITT population for analysis	N=148(97)	N=154(100)	N=160(99)	N=152 (97)	N=150(99)		
Patient Overall Health Assessment Mean change (SD)	-0.95(1.21)	-0.95(1.30)	-0.65(1.12)	-0.37(1.04)	-0.88(1.31)	<0.0001	0.0158
WOMAC LK 3.1 stiffness ITT population for analysis	N=150(99)	N=154(100)	N=161(100)	153(97)	N=151(100)		
WOMAC LK 3.1 stiffness Mean change (SD)	-2.30(2.00)	-1.93(2.01)	-1.48(2.07)	-1.52(2.05)	-2.07(2.02)	0.1120	0.0347
Patient Global Assessment ITT population for analysis	N=150(99)	N=154(100)	N=161(100)	N=155(99)	N=151(100)		
Patient Global Assessment Mean change (SD)	-1.53(1.27)	-1.36(1.19)	-1.07(1.10)	-1.01(1.18)	-1.42(1.29)	0.0165	0.0181

PEN+OD- PENNSAID® plus oral diclofenac
PEN+OP-PENNSAID® plus oral placebo
VC+OP- vehicle control (45.5% DMSO) plus oral placebo
P+OP- topical placebo plus oral placebo
P+OD- topical placebo plus oral diclofenac

It is notable that while improvement was consistent across the different outcome measures the level of improvement was modest given that the additional reduction in pain provided by PENNSAID treatment over placebo was small compared to the improvement seen with placebo. For pain the effect size of PENNSAID was 1.3 (6.0 minus 4.7) compared to a reduction in pain with placebo of 4.7. Thus the additional reduction in pain with PENNSAID was approximately one-quarter (28%) the reduction seen with placebo alone. Nonetheless the effect size achieved with PENNSAID was approximately three-quarters the effect size of oral diclofenac (1.3/1.7 or 76%).

Study PEN-03-112 also allows an assessment of the contribution of the vehicle DMSO 45.5%. The data suggest that vehicle alone has little clinical activity in improving signs

and symptoms of knee OA. Pain improved similarly (4.7 units with both treatments) with vehicle control as with placebo, as did physical function (12.1 with vehicle control vs. 12.3 with placebo). The only exception was POHA, where more improvement was seen with vehicle control than with placebo (0.65 vs. 0.37 units). These results indicate that the active ingredient in PENNSAID is diclofenac and that the DMSO has little if any contribution by itself to clinical efficacy.

To further assess the clinical significance of the results and their generalizability several exploratory analyses were carried out. The responses to PENNSAID were analyzed based on the OMERACT-OARSI criteria for responders in OA trials. More patients achieved OMERACT-OARSI response criteria with PENNSAID than placebo (75% vs. 61%), suggesting that the responses to PENNSAID were clinical meaningful. Analyses of patients characterized based on baseline demographics and baseline disease characteristics did not reveal any subset of patients lacking a response to PENNSAID. These results indicate that the clinical benefits of PENNSAID were broadly distributed in the patient population.

The results of study 109-US also showed statistically significant benefits for PENNSAID with respect to the co-primary endpoints of WOMAC pain, physical function and patient global assessment (Table 3). Similar to the results in study PEN-03-112, the clinical benefits of PENNSAID were modest. For example the effect size of PENNSAID for WOMAC pain was 1.5 (5.9 -4.4 units) compared to the 4.4 unit improvement in pain observed with placebo alone. Nonetheless, an exploratory analysis showed that PENNSAID treatment was associated with a higher proportion of OMERACT-OARSI responders, indicating that the benefits were clinically meaningful.

Table 3: Efficacy analysis in study RA-CP-109-US. Mean change of the scores from baseline to final visit, comparison between the groups, ITT population, n=326.

Variable	PENNSAID N=164	Vehicle control (45.5% DMSO) N=162	p-value
WOMAC LK 3.1 pain score Mean change (SD)	-5.9(4.7)	-4.4 (4.4)	0.0017
WOMAC LK 3.1 physical function Mean change (SD)	-15.3(15.2)	-10.3 (13.9)	0.0024
WOMAC LK 3.1 stiffness Mean change (SD)	-1.8(2.1)	-1.3(2.0)	0.0086
Patient Global Assessment Mean change (SD)	-1.3(1.2)	-1.0(1.1)	0.0052
OMERACT – OARSI responders	120/163 (74%)	94/159 (59%)	

3. Review of Safety

3.1. Extent of Exposure

The extent of exposure to PENNSAID in the phase 3 program is shown in Table 4. Overall, safety data are available on 897 patient, of whom 302 were treated for 85 days or longer.

Table 4: Patient exposure to PENNSAID in phase 3 trials

Study#	Total No patients exposed with available data	Total No patients exposed	Number of patients exposed to PENNSAID for specific durations								
			0-14 days	15-28 days	29-42 days	43-56 days	57-70 days	71-84 days	85-90 days	>90 days	Unknown
102-93-1	41	41	5	1	33	2	0	0	0	0	0
107-96	84	84	7	71	6	0	0	0	0	0	0
108-97	50	50	6	8	33	3	0	0	0	0	0
RA-CP-109	106	107	7	8	74	17	0	0	0	0	1
RA-CP-109-US	160	164	9	11	8	7	4	42	76	3	4
RA-CP-110	305	311	26	27	19	19	12	57	140	5	6
PEN-03-112	151	154	7	12	8	4	8	34	78	0	3
Total	897	911	67	138	181	52	24	133	294	8	14
Cumulative	897	911	897	830	692	511	459	435	302	8	14

3.2. Deaths

Overall, there were 10 deaths in the PENNSAID clinical development program. Three deaths occurred in the controlled trials. One patient who was exposed to PENNSAID in a phase 1 sensitization study died of a malignancy of unknown type. One 63 year old male patient receiving vehicle control with a history of hypertension and diabetes had an acute MI. The third patient died of complications of an acute MI taking oral diclofenac in study RA-CP-110.

Seven deaths occurred in the long-term studies. Most were cardiovascular in origin. Examination of the individual cases showed that they occurred in patients at known risk of cardiovascular events.

Overall, the pattern of deaths in the controlled and uncontrolled long-term studies does not suggest that they are related to treatment with study medication.

3.3. Serious adverse events

As shown in Table 5, serious adverse events (SAEs) occurred at a similar rate among patients receiving PENNSAID (10 or 911, 1%) as those receiving placebo (5 of 332, 1.5%), oral diclofenac (5 of 462, 1%) or the combination of oral diclofenac and topical PENNSAID (3 of 152, 2%). No individual type of SAE occurred in more than 2 patients in the PENNSAID group. In view of the known cardiovascular risks with NSAIDs it is important to examine these cases in more detail. Two SAE's of coronary thrombosis were seen in the PENNSAID group (2 of 911) compared to none with placebo (0 of 332) and 1 with oral diclofenac (of 462). In view of the small numbers and unequal denominators it is impossible to make conclusions about the relative risk of cardiovascular thrombotic events with topical diclofenac (PENNSAID) as compared to oral diclofenac. However, no clear pattern indicating a safety signal for cardiovascular events was seen with PENNSAID in the clinical development program.

Table 5: Serious Adverse Events in patients treated with PENNSAID® in seven phase III trials.

TREATMENT GROUP	PENNSAID N=911	ORAL DICLOFENAC N=462	PENNSAID & ORAL DICLOFENAC N=152	PLACEBO N=332	VEHICLE CONTROL N=442
CARDIOVASCULAR	4	1	1	0	1
Coronary thrombosis requiring treatment	2	1	1		
Chest pain requiring evaluation	1				1
Ablative cardiac surgery (planned)	1				
CEREBROVASCULAR	2	0	1	1	1
CVT requiring treatment	2		1	1	
Transient ischemic attack					1
GASTROINTESTINAL		2			1
Upper GI bleeding		1			
Lower GI bleeding		1			
Enteritis					1
ABNORMAL LFTs	0	1	0	0	0
CANCER	1				
INFECTIONS					
Pneumonia				1	
Cellulitis			1		
MUSCULOSKELETAL	1	1	0	2	0
Baker's cyst		1			
Prosthesis hip dislocation				1	
Hip fracture				1	
Right leg and foot pain	1				
ACCIDENTAL INJURY(fall)	1				
ALLERGIC REACTION	1				
ANEMIA				1	

3.4. Adverse events of interest

Since DMSO has been shown in some animal studies to be associated with lens opacities patients were monitored closely for the development of cataracts in the PENNSAID clinical development program. The safety database was examined critically for cataracts and other ophthalmologic adverse events. However, assessing increases from the background rate of cataracts is difficult in these studies because of an elevated background rate in this older patient population.

Two cases of retinal detachment were seen in the PENNSAID program. One patient was receiving oral diclofenac plus oral placebo (2.3% DMSO). The other patient had a history of cataract surgery and developed 70% retinal detachment in a long-term treatment study. These cases were reviewed by the Opthalmology consultant who concluded that there were no factors to suggest that these adverse events were related to study drug.

In study PEN-03-112 patients underwent ophthalmologic exams at baseline and at the end of study. The proportion of patients with new cataracts was similar in the PENNSAID and other treatment arms.

Finally, the proportion of patients developing new cataracts as reported events was compared to historical rates in the literature. These analyses did not indicate an elevated rate of cataract formation compared to the expected rate.

3.5. Other adverse events

Overall, the adverse event profile of PENNSAID consisted primarily of application site reactions and adverse events known to be associated with the NSAID class of drugs. In the seven phase 3 trials application site reactions were seen more frequently with PENNSAID than control: 32% vs. 5% for dry skin; 9% vs. 2% for contact dermatitis and 4% vs. 2% for pruritus. Application site reactions were generally mild-moderate in severity and resolved upon discontinuation of the product. Moderate application site reactions consisted of contact dermatitis with vesicles, which was seen in 10% of patients in the long-term treatment trial PEN-03-112E. Application site reactions were the most common cause of dropout due to toxicity among PENNSAID-treated patients.

GI adverse events, edema and liver enzyme elevations are known toxicities associated with NSAIDs. Adverse events in the GI system were seen more frequently with PENNSAID than control, including dyspepsia (8% vs. 4%), abdominal pain (6% vs. 3%), flatulence (4% vs. <1%), diarrhea (4% vs. 1%), nausea (4% vs. 1%) and constipation (3% vs <1%). Edema and peripheral edema were also more frequent with PENNSAID (6% vs. 3%). Liver enzyme elevations were observed more frequently with PENNSAID than placebo (2% vs. <1%) in study PEN-03-112 but not as frequently as with oral diclofenac (7%).

Since many patients who would receive PENNSAID if it is approved may also receive comcomitant oral NSAIDs, including oral diclofenac, it is important to consider toxicities that may be associated with combination treatment. Since study PEN-03-112 contained a combination oral diclofenac/PENNSAID arm and a PENNSAID alone arm, the safety results provide an opportunity to assess the safety of combination treatment. Several adverse events emerged as occurring more frequently with combination treatment. Rectal bleeding was observed in 5 of 152 patients receiving oral diclofenac/PENNSAID combination and 1 in the PENNSAID alone group. Detailed review of the cases showed that they were generally mild and self-limited and that patients were kept on study medication despite the rectal bleeding. Other adverse events observed more frequently with the combination than with either PENNSAID or oral diclofenac include diarrhea (8% with combination, 1% with PENNSAID, 5% with oral diclofenac) and application site contact dermatitis (8% with combination, 3% with PENNSAID, <1% with oral diclofenac).

3.6. Laboratory toxicities

Only minor, generally transient changes in laboratory parameters were seen associated with PENNSAID treatment.

4. Chemistry, Manufacturing and Controls

The chemistry reviewer for this application was Dr. Sue-Ching. She identified no issues that would interfere with an approval. Furthermore there were no outstanding CMC issues remaining from the last NDA submission.

5. Pharmacology/Toxicology Issues

The sponsor did not conduct animal toxicology studies of PENNSAID. Instead, they submitted their application under 505(b)2, relying on animal studies reported with Voltaren. At the time of this review, the Pharmacology/Toxicology review team is still in the process of deciding whether dermal carcinogenicity and photococarcinogenicity studies should be required. Given that oral diclofenac is an approved product and is not carcinogenic and that the safety database for PENNSAID, including post-marketing data from the United Kingdom and Canada, does not indicate a concern with carcinogenicity of this product, this reviewer believes that animal carcinogenicity and photococarcinogenicity are not needed before approval of this product.

6. Clinical Pharmacology

Review of the Clinical Pharmacology portion of this application did not reveal any concerns. Dr. David Lee reviewed studies submitted to assess the bioavailability of diclofenac in PENNSAID. A single-dose study compared blood levels of diclofenac following topical PENNSAID or oral diclofenac. The study showed that maximum blood levels of diclofenac with PENNSAID were 187-200 times lower than with oral diclofenac sodium.

7. Study site inspections

As of the time of writing study site inspections have not been completed.

8. Conclusions

The clinical development program for PENNSAID demonstrated consistent, modest efficacy in the treatment of knee OA. In two pivotal trials, statistically persuasive results demonstrated efficacy for the key endpoints of pain, physical function and patient global assessment. Other, less well-designed studies, showed similar results. Sensitivity analyses using a variety of imputation techniques showed that the results were not biased by missing data. Benefits were seen in all subsets of patients examined with respect to baseline demographics and baseline disease activity parameters.

Based on analysis of the safety database submitted, the main safety concerns for PENNSAID are administration site reactions, particularly dermatitis and dermatitis with vesicles, and adverse events known to be associated with drugs in the NSAID class. While it might be expected that systemic toxicities of PENNSAID would not be seen given the low observed blood levels of diclofenac with PENNSAID (187-200 fold lower than with oral diclofenac), the clinical trials showed higher rates of GI toxicities, liver enzyme elevations and edema. All these events occurred at rates lower than, or similar to, the rates seen with oral diclofenac.

An important consideration for labeling is providing appropriate precautions about the use of PENNSAID in combination with oral NSAIDs. Data from the clinical development program indicate that adverse events seen more frequently with

combination treatment include rectal bleeding, diarrhea and application site contact dermatitis.

9. Recommendations

At the time of this writing, clinical site inspections have not been completed. Assuming that the clinical site inspections do not reveal serious concerns about the conduct of the clinical trials or the reporting of data, I recommend approving PENNSAID with appropriate labeling.

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/s/

Jeffrey N Siegel
12/6/2006 01:12:36 PM
MEDICAL OFFICER

MEDICAL OFFICER SAFETY REVIEW

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Product (HFD-550)

NDA: 20-947

Drug name: Pennsaid Topical Solution
(1.5% w/w diclofenac sodium)

Sponsor: Dimethaid International, Inc.

Date of submission: August 07, 2002

Date of review: August 06, 2002

Reviewer: Tatiana Oussova, MD, MPH

Integrated Review of Safety

PENNSAID: NDA #20-947

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INTEGRATED REVIEW OF SAFETY

I. Introduction and Background

This medical officer review is a safety review of the Pennsaid topical solution (diclofenac sodium) that was done as part of the FDA's overall review of Dimethaid International, Inc.'s submission of NDA 20-947.

Pennsaid is a topical solution containing diclofenac sodium 1.5% w/w in a carrier solution that contains dimethyl sulfoxide (DMSO) 45.5% w/w, propylene glycol, glycerol and ethanol.

Diclofenac is a bezeneacetic acid derivative that belongs to the non-steroidal anti-inflammatory class of drugs (NSAIDS). It is a non-selective NSAID which inhibits both COX-1 and COX-2 isoforms of the enzyme cyclooxygenase. Diclofenac is a well-known drug that has been marketed in the United States since 1986 as a sodium salt prescription drug under the trade name Voltaren. It is indicated for the acute and chronic treatment of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA). The immediate-release formulation of diclofenac is indicated for the management of pain in primary dysmenorrhea. Only oral formulations of the drug have been approved for use in the United States as an analgesic, though the topical formulation of the drug has been approved in some European countries under the name Voltaren Emulgel. It contains 1.16% diclofenac and is recommended for the relief of pain from contusions, sprains, osteoarthritis, tendinitis.

Adverse effects of oral diclofenac include both tolerability issues including upper gastrointestinal upset as well as more serious potential toxic effects such as ulceration with bleeding or perforation; serum elevation of liver transaminases as well as severe hepatic reactions such as liver necrosis, fulminant hepatitis and liver related deaths; elevated blood pressure; deterioration of renal function; and fluid retention.

The topical formulation of diclofenac sodium (Pennsaid) was developed in attempt to minimize or eliminate these side effects yet preserve the therapeutic efficacy in the treatment of OA pain of the knee joint [redacted] b(4)

DMSO is used in the above formulations as a penetrating solvent to accelerate absorption of the topical diclofenac. The only US-approved formulation of DMSO for human use is 50 % w/w aqueous solution (RIMSO-50) for the treatment of symptoms of interstitial cystitis by intravesical instillation of 50 mL of RIMSO every two weeks.
According to the label, DMSO can initiate the liberation of histamine and there have been occasional hypersensitivity reactions with topical administration of DMSO. Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of DMSO chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving DMSO should have liver and renal function tests, and complete blood count done.

DMSO is approved for veterinarian use. The following are the FDA requirements for such use:

a) Specifications. Dimethyl sulfoxide contains 90 % of dimethyl sulfoxide and 10 % of water ... (c) Conditions of use. (1) It is used or intended for use as a topical application to reduce acute swelling due to trauma: (i) In horses administered 2 or 3 times daily in an amount not to exceed 100 ml per day. Total duration of therapy should not exceed 30 days. (ii) In dogs administered 3 or 4 times daily in an amount not to exceed 20 ml per day. Total duration of therapy should not exceed 14 days. (2) Not for use in horses and dogs intended for breeding purposes nor in horses slaughtered for food. Other topical medications should only be used when the dimethyl sulfoxide treated area is thoroughly dry. Do not administer by any other route (3) For use by or on the order of a licensed veterinarian.

This reviewer conducted a literature search about DMSO safety using the TOXNET (TOXLINE, DART, HSDB) database. It suggested that DMSO is a skin, eye, and respiratory tract irritant. DMSO may cause urticaria, and there have been rare reported cases of anaphylaxis. There are no therapeutic or toxic blood levels established. Skin contact results in irritation with redness, itching, sometimes scaling. Inhalation exposure may be sufficiently high to cause headaches, dizziness, and nausea. It may cause elevation in liver enzymes, transient hemolysis with hemoglobinuria. A dose dependent hematuria is possible. All of these suggest there may be systemic exposure with topical application.
Review of the information available in the published literature indicates that DMSO should be viewed as an ingredient with its safety profile as well as pharmacologic effect.

1. References in the medical literature:

Coye M, Belanger PL; Health Hazard Evaluation Report No. 80-98-790. San Francisco General Hospital, San Francisco, CA. NIOSH 00114015 NTIS PB82-183943 Cincinnati, OH: NIOSH, Hazard Eval Tech Assist Branch (1981)

Dimethyl sulfoxide exposure may result to hospital and veterinary personnel administering dimethyl sulfoxide as a drug and human patients receiving treatment. Inhalation exposure may be sufficiently high to cause headaches, dizziness, and nausea if the area is not well ventilated.

Haddad, L.M., Clinical Management of Poisoning and Drug Overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Co., 1990.

To investigate possible side effects of chronic exposure to dimethyl sulfoxide, 20 volunteers were painted with 9 ml of 90% dimethyl sulfoxide over the entire trunk, once daily for a period of 26 weeks. Neither clinical nor laboratory investigations showed adverse effects of the drug. However, most subjects did experience the well-known DMSO induced, disagreeable oyster like breath odor, to which they eventually became insensitive. One fatality due to a hypersensitivity reaction has been reported.

Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.

Skin contact results in primary irritation with redness, itching & sometimes scaling. Urticarial wheals are not uncommon.

Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988.

Nausea, vomiting, abdominal cramps, chills, chest pains, and drowsiness have been reported as well as erythema, itching, garlic odor on the breath (lasts a few minutes), and transient hemolysis with hemoglobinuria. Nephrotoxicity has not been found after use of dimethyl sulfoxide as a penetrating solvent for some topical medicaments.

Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2002; CCIS Volume 113, edition exp August, 2002. Hall AH & Rumack BH (Eds):TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2002; CCIS Volume 113, edition exp August, 2002.

Summary of acute exposure: 1. DMSO has shown very few toxic symptoms in humans. The most common are nausea, skin rashes, headache, and an unusual garlic-onion-oyster smell in body and breath. 2. DMSO is a skin, eye, and respiratory tract irritant. It may cause skin irritation and reddening if spilled on clothing and allowed to remain. DMSO readily penetrates the skin and may carry other dissolved chemicals into the body. 3. DMSO may cause urticaria and, rarely, anaphylaxis. 4. DMSO is an experimental teratogen and also causes other reproductive effects in experimental animals. 5. Dyspnea and increased symptoms of bronchial asthma are possible.

With therapeutic use 1. Headache, dizziness, and sedation have been seen. 2. Nausea, vomiting, diarrhea, anorexia, and constipation may occur. 3. May see elevated liver enzymes. 4. A dose dependent hematuria is possible.

Genotoxicity : DMSO tested positive for mutagenicity in bacteria and caused DNA damage in a mouse model (RTECS, 1991).

There are no therapeutic or toxic blood levels established.

Amdur, M.O., J. Doull, C.D. Klaasen (eds). Casarett and Doull's Toxicology. 4th ed. New York, NY: Pergamon Press, 1991.

Dermal application resulted in 50-60 mg % in blood in 4-8 hr; half-life 11-14 hr. 220-340 mg % reported following oral admin of 1000 mg/kg; half-life 20 hr.

Sunshine, I. (ed.). CRC Handbook of Analytical Toxicology. Cleveland: The Chemical Rubber Co., 1969.

Little information is available concerning the mechanism by which DMSO enhances skin permeability. ... It has been suggested that DMSO (1) removes much of the lipid matrix of the stratum corneum, making holes or artificial shunts in the penetration barrier; (2) produces reversible configurational changes in protein structure brought about by substitution of integral water molecules; and (3) functions as a swelling agent.

II. Brief Statement of Findings

Findings of concern that require further study include:

- DMSO should be viewed as an ingredient with its safety profile as well as pharmacologic effect.
- Reported rates from uncontrolled trials that are far below clinical trials raise concern over ability of such data to inform about safety profile
- In general, it appears that skin-related adverse reactions represent a significant problem with both Pennsaid and DMSO but the long-term safety data derived from

two uncontrolled studies is not adequate to fully assess long-term skin-related safety of study medications (both Pennsaid and DMSO)

- The number of cardio-vascular events, including two fatal MI, occurred with the use of Pennsaid/DMSO 45.5%. Potential of either diclofenac or DMSO causing it should be evaluated more closely.
- There are a number of withdrawals due to GI side effects among Pennsaid/DMSO 45.5% treated patients. Two cases of melena in DMSO 45.5% treated patients raise a concern about potential DMSO GI side effects. This requires further investigation. Further clarification of the adverse events seen with the use of DMSO 45.5% alone is needed.
- Two cases of discontinuation from the study due to blurred vision need further clarification. There are reports of lens opacities in reviewed literature observed in different animal species with the chromic use of DMSO. There are no adequate chronic use studies in human. Ophthalmologic evaluation should be included in future study.
- The only laboratory values submitted by the sponsor are for studies #102-93-1 and #107-96. For two pivotal studies #109 and #109-US the sponsor did not submit any laboratory data. Summary of lab data was derived from these two trials of 4-6 weeks duration therefore no conclusions can be drawn about long-term safety. The absence of long-term (> 3 months) lab data is of major concern.
- LFT and hematologic abnormalities (hemoglobin, platelets, white blood cells) rates as reported are potentially meaningfully higher in the Pennsaid /DMSO 45.5% treated subjects compare to the 4.55% treated subjects. It may represent statistical variability and reviewer cannot draw conclusions. However, both Pennsaid and DMSO 45.5% rates may suggest safety signal with DMSO. If so, limitation in duration of study prevents full characterization.
- The reviewer's analysis of Glucose level raises some concerns as well.
- Given the low power to detect statistically significant difference, trends must be the basis for safety assessment. This is particularly true for a drug that includes a component such as DMSO for which there are very little controlled data.
- Synergistic effect of Pennsaid and DMSO cannot be excluded.
- Drug-drug interactions have not been addressed. Co-use with other NSAIDs is of major concern.
- Pennsaid use in patients with renal or hepatic impairment has not been addressed
- Racial minorities' groups are underrepresented across all trials that create potential limitations for generalizability of the submitted claims.

III. Materials Utilized in the Review

In support of this application, the sponsor submitted for Agency review the following safety information:

1. The safety database containing 3,681 subjects generated from a total of 14 trials (see Table #1 of clinical review for details):

a. Three clinical pharmacology studies (#106-95; #102-93-1, PK sub-set; #RA-CP-109-US, PK sub-set)

b. Four phase I Skin irritation/photosensitization studies (#100-89; #101-89-2; #103-93-2; #104-93-3)

c. Five phase III studies (#102-93-1; #107-96; #108-97; # RA-CP-109; #RA-CP-109-US)

d. Two uncontrolled clinical studies (open label study #105-95; open label multi-site study through Emergency Drug Program-EDR)

2. Case-report forms of serious adverse events

3. Diclofenac sodium label

4. Dermatologic safety review (see attached Appendix #1)

5. A summary of foreign postmarking surveillance reports collected from FDA's Adverse Events Reporting System (AERS) for topical formulations of diclofenac for the period of 1988 through June 27, 2002 (see attached Appendix #2)

6. The results of worldwide literature search of published clinical safety reports on diclofenac sodium and DMSO

III. Description of Patient Exposure

1. Total exposure

Table #1 of the medical review by Dr. James Witter provides the total number and type of studies, number of subjects or patients at given duration, and dose.

Drug exposure by the **total amount of compound** being used by individual patients during treatment is summarized in a **Table # 22** of Dr. James Witter review.

The following table shows the total number of patients exposed to Pennsaid:

Table #1: Enumeration of Patients Exposed to Pennsaid in Development Program (Sponsor's table #4a, Vol. 1.59 p. 11)

Study Number	Number Exposed	Additional Planned Exposures
a. Clinical Pharmacology		
102-93-1	(12*)	0
106-95	6	0
RA-CP-109-US	(23*)	0
Total number of patients exposed to PENNSAID® in clinical pharmacology studies = 41 (35)*		
b. Controlled Trials		
100-89	25	0

101-89-2	223	0
102-93-1	39	0
103-93-2	25	0
104-93-3	27	0
107-96	84	0
108-97	50	0
RA-CP-109	107	0
RA-CP-109-US	164	0
Total number of patients exposed to PENNSAID® in controlled trials = 744		
c. Uncontrolled Trials (months)		
105-95	2654	0
EDR	244 (30*)	0
Total number of patients exposed to PENNSAID® in uncontrolled trials = 2898 (30)*		
d. Other Indications		
N/A		

TOTAL = 3618

* Refers to the number of patients exposed to Pennsaid in this trial, that were also counted in another trial

Clinical pharmacology studies: (#102-93-1; #106-95)=**41**(35 of them were counted in other trials)

Controlled trials: (#100-89; #101-89-2; #102-93-1; #103-93-2; #104-93-3; #107-96; #108-97; #RA-CP-109; #RA-CP-109-US)=**744**

Uncontrolled trials: (#105-95; EDR)=**2868** (30 were counted in other trials)

In the uncontrolled trials, of the **2898** patients exposed to Pennsaid, **1565** were exposed for less than one month, **440** patients were exposed for 1 to 3 months, **260** were exposed for 3 – 6 months, **227** were exposed for 6 to 12 months and **406** were exposed for more than 12 months. (Clinical Data Electronic Submission, p. 27)

Table #2: Number of Patients Exposed to PENNSAID® Altogether and For Specified Periods of Time (Sponsor's table #5b, Vol. 1.59 p. 67-68)

Study Number	Total # Patients Exposed	Number of Patients Exposed							
		≤ 1 day		2 - 7 days		8 - 30 days		> 30 days	
		M	*F*	*M*	*F*	*M*	*F*	*M*	*F*
a. Clinical Pharmacology									
102-93-1	(12)[1]	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(9)
106-95	6	5	1	0	0	0	0	0	0
RA-CP-109-US	(23)**	0	0	0	0	0	(1)	(8)	(14)

b. Controlled Trials									
100-89	25	0	0	0	1	13	11	0	0
101-89-2	223	4	3	3	2	111	96	2	2
102-93-1	41	0	0	2	1	3	0	7	28
103-93-2	25	13	12	0	0	0	0	0	0
104-93-3	27	0	0	0	0	11	8	5	3
107-96	84	0	0	2	2	49	30	1	0
TOTALS	***431***	***22***	***16***	***7***	***6***	***187***	***145***	***15***	***33***

Study Number	Total # Patients Exposed	Number of Patients Exposed							
		0 – 7 days		8 - 35 days		36 - 42 days		> 42 days	
		M	*F*	*M*	*F*	*M*	*F*	*M*	*F*
b. Controlled Trials (cont'd)									
108-97	50	0	5	0	10	3	29	0	3
RA-CP-109	106	0	3	7	8	31	40	13	4
RA-CP-109-US	160	2	5	3	12	2	4	40	92
TOTALS	***316***	***2***	***13***	***10***	***30***	***36***	***73***	***53***	***99***

[1]This number refers to the number of patients exposed to PENNSAID® in this trial that were also counted in study #102-93-1 under "Controlled Trials".
**This number refers to the number of patients exposed to PENNSAID® in this trial, that were also counted in study #RA-CP-109-US under "Controlled Trials".

Study Number	Total # Patients Exposed	Number of Patients Exposed														
		0 - 1 months			1 - 3 months			3 - 6 months			6 - 12 months			12+ months		
		M	*F*	*NR*	*M*	*F*	*NR*	*M*	*F*	*NR*	*M*	*F*	*NR*	*M*	*F*	*NR*
c. Uncontrolled Trials																
105-95	2654	496	840	28	128	300	3	80	171	3	94	122	1	168	220	0
EDR / 105-95	30	0	0	0	0	0	0	1	1	0	2	8	0	7	11	0
EDR	214	81	120	0	3	6	0	2	2	0	0	0	0	0	0	0
TOTALS	***2898***	***577***	***960***	***28***	***131***	***306***	***3***	***83***	***174***	***3***	***96***	***130***	***1***	***175***	***231***	***0***

Comments:

- The majority of patients were exposed to Pennsaid in uncontrolled trials.
- According to ICH guidelines, "the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300 to 600 patients exposed to a study drug for 6 months should be adequate". As ICH guidelines also state, "there is concern that, although they are likely to be uncommon, some AEs may increase in frequency or severity with time or that some serious AEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of AEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent

a judgement based on the probability of detecting a given AEs frequency level and practical considerations. 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use".

- The data on long-term exposure to Pennsaid (6 month or longer) was derived from uncontrolled trials EDR and #105-95.The rates of adverse events reported from uncontrolled trials (none from EDR and very low rates from trial #105-95-far below the rates reported from controlled trials) raise serious concerns that underreporting presents a significant problem in the uncontrolled setting, therefore the safety data derived from uncontrolled trials cannot be viewed as sufficient to assess the long-term safety of Pennsaid. The problem of underreporting could be due to inadequate monitoring or poor patient compliance, among other reasons.
- It is impossible to make any conclusions on whether the dosage used in uncontrolled trials was comparable to the one intended for clinical use.
- Other deficiencies noted: In the above table the sponsor combined single application studies with multiple application studies. The sponsor also combined the exposure of different application sites- hand and knee- in one table. Table above lists a total of 431 patients involved in trials #100-89, #101-89-2, 102-93-1, 103-93-2, 104-93-3 and 107-96. Sponsor's table #5a (Vol. 1.59, p. 12), which is a short version of sponsor's table #5b (Vol. 1.59, pp.67, 68), has 423 as a total number of patients exposed to Pennsaid in the above-mentioned trials.
- The study #100-89 included simultaneous application of Control (diclofenac 10%), Pennsaid, Placebo-1 (DMSO 45.5 %) and Placebo-2 (DMSO 4.55%) applied to four different sites. This significantly increases expose to diclofenac therefore should be analyzed separately.
- The inconsistency among studies in defining duration of expose makes their comparison difficult. Also, the amount of study drug calculated as **patient x days of exposure** does not equal to the amounts of drug calculated as **joint x days of exposure** because one patent could use the study medication to treat one or both knee or wrist joints.

Conclusions:

There is no similar information about exposure to **DMSO.**

2. Demographic characteristics of exposed population

The following table lists the demographic characteristics of the subjects exposed to Pennsaid in all studies.

Table #3: Demographic and Other Characteristics of the Study Population Exposed to PENNSAID®
(Sponsor's table#8a, Vol. 1.59 p. 15)

Study	Mean Age	Sex (M:F)	Race									Mean Body Weight (lbs)
			White	Black	Hispanic	Indian	Asian	Native North American	Spanish	Other	Not Recorded	
a. Clinical Pharmacology												
RA-CP-109-US	63	15:8	20	3	0	0	0	0	0	0	0	202.8
106-95	48.7	5:1	4	1	0	0	0	1	0	0	0	183.3
102-93-1	63.1	3:9	11	0	0	1	0	0	0	0	0	175.4
b. Controlled Trials												
100-89	48.4	13:12	16	0	9	0	0	0	0	0	0	N/A
101-89-2	44.7	119:104	91	68	53	0	5	0	0	5	1	N/A
102-93-1	60.1	8:33	39	1	0	0	0	1	0	0	0	180.2
103-93-2	62.8	13:12	14	0	9	1	0	0	0	1	0	N/A
104-93-3	47.0	16:11	24	0	3	0	0	0	0	0	0	N/A
107-96	62.5	32:52	79	1	0	0	4	0	0	0	0	178.9
108-97	64.7	3:47	48	1	0	0	1	0	0	0	0	69.4 kg
RA-CP-109	65	51:56	88	8	0	0	3	0	0	8	0	89.9 kg
RA-CP-109-US	63.4	51:113	142	18	3	0	1	0	0	0	0	204 lbs
c. Uncontrolled Trials												
EDR	58	96:148	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
105-95	55.0	681:1119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Of all subjects exposed to Pennsaid across all study groups, most patients were middle-aged, with a mean range ranging from 44.7 to 65 yrs. of age. The most common race of patients exposed to Pennsaid in each of the studies was white with a number of patients that were black or Hispanic.

Comments:

- It appears that both genders are adequately presented in controlled trials
- It appears that elderly population is adequately represented in controlled trials
- Racial data is not available for uncontrolled trials. Review of the demographic parameters of the population in individual studies reveals that except for one study (#101-89-2), there were almost no Black and Hispanic patients included in the studies. Native Americans and Asians are significantly underrepresented across all studies. This might limit generalizability of the studied claims.

V. Safety Findings from Clinical Studies

1. Evaluation and Elicitation of adverse events

In the Phase I safety studies, at each visit, the site of application was assessed and graded for adverse application site reactions, according to a specified questionnaire, as specified in each protocol. The investigator or coordinator also recorded any other adverse event reported by the patient.
In the Phase III controlled clinical efficacy trials, **#102-93-1, #107-96, #108-97, #RA-CP-109 and #RA-CP-109-US**, adverse events were documented from three sources.
1. Each patient kept a daily diary in which s/he was to record "any abnormal event you think may be related to the use of the study medication...". The severity was not recorded at each clinic visit. 2. The site of application was assessed and graded for adverse application site reactions, according to a specified questionnaire. The investigator or coordinator asked in an open-ended fashion about any adverse events.
3. In addition, in study **#107-96, #108-97, #RA-CP-109 and #RA-CP-109-US**, the coordinator asked about specific adverse events from a checklist. (Where both the patient and investigator commented on the same event, it was included only once.) The coordinator recorded each adverse event on the case report form, which were coded according to COSTART.
In the open-label safety study **#105-95**, at each clinic visit the investigator or coordinator asked about specific adverse events from a checklist. The coordinator recorded each adverse event on the case report form, which we coded according to COSTART.

As sponsor states, no statistical comparison has been done. Rather, an estimation of significance is based on a difference between Pennsaid and the control or placebo.

Comment:

- There are different methods of adverse event assessment within the studies and between studies. This makes it hard to combine data from different studies.
- It is unclear what follow-up was provided to the patients with adverse events.

2. Deaths and Adverse Event Causing Withdrawals

Table #4 displays the deaths and adverse events that caused withdrawals of patients exposed to Pennsaid.

Table # 4: Display of Deaths, Adverse Dropouts and Other Serious Events for Patients Exposed to Pennsaid
(Sponsor's table # 7, item 3 Application Summary, Clinical documents, Electronic Submission)

Study No.	Patient No.	Total Dose (mL)	Duration (days) of Treatment	Adverse Experience
Controlled Trials				
100-89	6	0.4	2	patient developed erythema and induration

101-89-2	19	0.8	8	site(s) developed erythema, induration and vesicles
	103	1.8	19	cancer, could not continue, died
	139	1.6	17	site(s) developed erythema, induration and vesicles
102-93-1	232	1 mL	4	Other - reaction to drug? increased pain
	307	QID	2	Lack of effect; poor tolerance to study medication; insufficient and/or unreliable patient co- operation; Other - pt anxious
107-96	1032		16	other-aphasia caused by CVA
	1040		15	other-redness, itchiness
	1054	1 mL	6	lack of effect, other - pain in shoulder and hip
	1069	QID	9	asthenia/palpitation
	1077		13	rash/pruritus/vesiculobullous rash
	4023		12	hospitalized for cardiac oblation for long-standing cardiac arrhythmia - did NOT drop-out
	4031		2	rash (knee)/arthrosis (knee)/face edema/dyspepsia/headache/malaise
	6006		5	pruritus/arthralgia
	6014		5	body odour/halitosis
108-97	02-001	0.125	12	dry skin
	02-014		22	face edema
	04-017		5	pruritus, dry skin, rash
	05-015		5	dry skin
	05-023		10	dry skin
	06-016		12	dry skin
	06-018		14	cardiovascular event (heart attack)
	07-012		9	back/neck pain
	07-016		6	dry skin, rash, pruritus, arthrosis
	09-012		42	lung cancer
RACP-109	01-013	1 mL	18	SAE - fractured ankle after fall
	03-005		13	pimple-like rash to knee, chest & nose
	04-011		15	sore shoulders; exacerbation of OA in shoulders
	08-005		34	face & hands pruritus
	09-005		24	skin peeling with redness left & right knee
	10-009		7	arthritic pain in back too severe to continue
	11-015		23	arthritic pain in back & shoulders unbearable
	14-009		11	dryness and flakiness to both knees
	16-007		36	rash in back of legs & behind knees
RA-CP-109-US	28-011		1	SAE - chest pain
	39-002		9	SAE – myocardial infarction
	05-011		48	rash left knee
	06-019		16	erythema on knees bilaterally
	06-031		52	rash bilaterally
	08-003		57	Blisters (small) both knees
	15-015		6	redness site of application
	21-017		2	nausea, abdominal discomfort
	33-005		1	dizziness, headache, tingling right knee
Uncontrolled Trials			**(months)**	
105-95	122	N/A	0-1	ulceration of arthritic nodules @ metacarpal phalangeal jnt.
	164	N/A	1-3	itching erythema
	240	N/A	6-12	Myocardial Infarction - deceased
	396	N/A	0-1	blistering of skin at R knee
	447	N/A	3-6	erythema, pruritus
	540	N/A	3-6	blurred vision

	597	N/A	6-12	asthma / wheezing - 1 - 10 minutes afterwards
	603	N/A	1-3	nasal congestion, dizziness, headache, general fatigue, taste
	618	N/A	1-3	heartburn epigastric pain, vomiting
	697	N/A	1-3	nausea, heartburn
	742	N/A	3-6	intense skin reaction
	765	N/A	3-6	skin rash - over site of application
	775	N/A	0-1	rash
	780	N/A	1-3	increased pain
	783	N/A	0-1	acute swelling of 2 finger joints** and skin*** irritation***
	804	N/A	1-3	slight scaling at site of appl.
	887	N/A	3-6	in hospital for urgent R hemicolectomy for Crohn's, anemia
	998	N/A	1-3	aggravation of back pain
	1015	N/A	0-1	skin pruritus - 1/2 hr. after tried in office on hands
	1017	N/A	1-3	urticaria and pruritus
	1085	N/A	0-1	skin rash
	1133	N/A	1-3	dizziness, shortened breath when increased dose from 20x1 to 20x2 knees qid
	1338	N/A	1-3	gastritis - (heartburn and epigastric pain) - taking NSAIDs and EC ASA
	1410	N/A	1-3	increased blurred vision
	1470	N/A	1-3	funny taste in mouth**, mucous in throat, upset stomach - pain epigastric***
	1474	N/A	1-3	increasing pain, leg felt very weak
	1490	N/A	6-12	intense erythema
	1540	N/A	0-1	redness on joints, dry skin, peeling
	1602	N/A	1-3	reddening and blistering of skin in area of L shoulder and R palm (use of apply)
	1603	N/A	0-1	local rash
	1608	N/A	3-6	burning sensation
	1613	N/A	1-3	foul oral taste, urticaria
	1632	N/A	6-12	acute myocardial infarction (death)
	1666	N/A	0-1	burning on appl. itching until dry, swelling by 2nd day,** knee locked by swelling***
	1730	N/A	1-3	skin irritation score of 3

* multiple events

** or *** relation to PENNSAID® is indicated in last column on same row

Study #101-89-2

Subject #103 dropped out of the study on March 25, 1996 due to cancer, which eventually lead to the subject's death. The subject's CRF reads, "**Patient contracted cancer** and could not continue, died." The patient's concomitant medications were not recorded, however, the medical history revealed no significant abnormalities.

Study #107-96

Patient #1032 (age: 74, sex: F) was admitted to the hospital with **aphasia and confusion secondary to a cerebrovascular accident**. This event was reported as severe. The patient had been using the study drug, Pennsaid, q.i.d for the 16 days prior to the event. During the week prior to the adverse event the patient documented that she "didn't sleep very good and feel tired." The patient discontinued using Pennsaid after the adverse event. The concomitant medication being used by this patient was Acebutolol Hydrochloride (200mg; BID), Acetaminophen (325mg; 1-2 Q4H PRN), Enteric Coated Acetylsalicylic Acid (325mg; OD), Loratadine-Pseudoephedrine (10mg; OD) and Spironolactone (25mg; OD). The patient had a **previous history of CVA** (a recovered left cerebral infraction) and high blood pressure.

Patient #4023 (age: 66, sex: M) was hospitalized for **cardiac ablation for long-standing cardiac arrhythmia,** as was noted in the CRF. This event was reported as moderate. The patient had been using the study drug, Pennsaid, q.i.d for the 12 days prior to the event. The patient continued using Pennsaid after the adverse event. The concomitant medication being used by the patient was Digoxin (0.25mg; 1 OD), Diltiazem Hydrochloride (120mg; 2 OD), Gemfibrozil 300mg; BID), Misoprostol (200mg; 1 OD), Oxazepam (1mg; ½ HS PRN), Warfarin Sodium (1mg; 4 OD). The patient had a previous history of cardiac arrhythmia for 20 years.

Study #108-97

Patient #06-018, treated with Pennsaid, experienced chest pain 9 days after the onset of study treatment and, subsequently, experienced a **heart attack 14 days after onset of treatment**. The investigator deemed the relationship of the event to the study drug to be remote. The patient was taking the following medication at the time of the event: levothyroxine, dorzolamide hydrochloride, tobramycin, salbutamol sulfate, fluticasone propionate, multiple vitamins & minerals; nitroglycerin, pravastatin sodium, ranitidine hydrochloride and acetylsalicylic acid for cardiac prophylaxis. The patient recovered from the heart attack but continued to have angina following the event.

Patient #09-012, treated with Pennsaid, was diagnosed with **cancer 42 days after starting treatment**. Chest x-ray revealed multiple pulmonary nodules and CT of thorax & abdomen revealed thoracic & abdominal lesions, without obvious "primary". The patient was taking the following medication at the time of the event: fluoxetine hydrochloride, atenolol, sennosides, levothyroxine, conjugated estrogens, nifedipine, ranitidine hydrochloride, acetylsalicylic acid/butalbital/caffeine, garlic, vitamin E, docusate sodium, acetylsalicylic acid/butalbital/caffeine and acetaminophen/oxycodone hydrochloride.

Study #RA-CP-109

Patient #B01-013, treated with Pennsaid, **fell off of a stepladder** while trying to open her window, **injuring her chest and right foot**. The patient was sent to the hospital where a cast was applied to the foot. The patient was also taking the following medication at the time of the event: trihexyphenidyl hydrochloride, beclomethasone dipropionate, ipratropium bromide/salbutamol sulfate, brompheniramine maleate/ phenylephrine hydrochloride/phenylpropanolamine hydrochloride, venlafaxine hydrochloride, fluticasone propionate, alandronate sodium, quinine sulfate and zopiclone.

Study #RA-CP-109-US

Patient **# 28-011**, treated with Pennsaid, was walking her dog when, her dog was attacked by another dog. After returning home she began to experience **chest pain**. She went to the ER on 02/06/01, and was admitted for overnight observation because she lives alone. The patient was released from hospital on ——— Cardiac enzymes were negative and a chest x-ray showed no evidence of disease. Assessment at the time of discharge stated

b(6)

that the symptoms were consistent with an episode of angina provoked by extreme emotional upset.

Patient # 39-002, treated with Pennsaid, experienced **chest pain**. This patient, with a **history of myocardial infarction in 1997**, woke up on the morning of ——— with chest pains. He was transported via ambulance to hospital for evaluation. The physician in cardiac unit stated that the patient showed no signs of a new myocardial infarction. The patient was admitted for observation and follow up tests and **had cardiac bypass surgery on** ———The patient's expected recovery is very good. The patient requested to stay in the study, with the agreement of his cardiologist. b(6)

Study #105-95

Patient #240 (age: 52, sex: F) experienced **a myocardial infarction resulting in death.** This event was considered severe. The patient had been using Pennsaid, for approximately **6½ months prior to the event**. The concomitant medications used by this patient were Digoxin (digoxin, 0.25mg; OD), Enalapril (enalapril maleate, 10mg; OD), Pravachol (pravastatin sodium, 20mg; OD) (this information was obtained from a follow-up report). It was noted by the investigator on the CRF that the patient's "severe coronary artery disease predated Pennsaid lotion".

Patient #1632 (age: 71, sex: M) experienced, what was presumed to be, an **acute myocardial infarction resulting in sudden death.** This event was considered severe. The patient had been using the study drug, Pennsaid, for approximately **10 months** prior to the event. The concomitant medications being used by this patient were Altace, Minocycline, Folic Acid, Methotrexate, Arthrotec, Prednisone, Tylenol, Amitriptyline and Synthroid (this information was obtained from a follow-up report).

Patient #887 (age: 55, sex: F) was admitted for surgery during the study. The CRF indicates that the patient was admitted "for urgent R hemicolectomy for Crohn's disease". This event was reported as moderate. The patient had been using the study drug, Pennsaid, for almost 2 months when she experienced the abdominal pain, etc., but did not have surgery until 3 months after the initial adverse event. The concomitant medications being used by the patient were Rubramin (cyanocobalamin), Nifedipine XL (nifedipine) and Novotriptyn (amitriptyline hydrochloride) (this information was obtained from a follow-up report). It was stated on the patient's CRF by the investigator that the adverse event that there was a "successful outcome post surgery. Now in good health."

Comments:

- There were a total of 64 (12 %) adverse event withdrawals due to Pennsaid use in controlled trials and 64 (2.4%) in open-label study #105-95. EDR did not report any AE's. The adverse event withdrawals related to Pennsaid are primarily composed of skin-related adverse events ranging from dry skin to blisters and skin ulceration.
- The other causes of adverse event withdrawals are as follows: Two cases of cancer (including one death) appear not to be related to the study medication. Two patients dropped out in uncontrolled trials due to blurred vision; one due to wheezing; ten due to heartburn, nausea and vomiting; one experienced dizziness and shortness of breath

with increasing dose. One patient developed blistering on a right palm used to apply the study medication. Myocardial infarctions and chest pain occurred in 5 patients; two of them resulted in death. One patient had a deterioration of existing Crohn's disease requiring surgery.

- There were three cases of death reported by the sponsor. One death was due to newly diagnosed cancer after 19 days of being on study medication. Considering very short exposure, it is unlikely that this death was related to the study medication. Two other deaths were due to myocardial infarction. Both deaths occurred in uncontrolled trials and apparently after prolonged use of study medication (6-12 months). One case was confounded by pre-existing heart conditions. It is difficult to establish a cause –effect relationship between the study medication and event. Only controlled trials can clarify this issue.
- There were cases of cardio-vascular events including CVA, TIA, non-fatal MI and chest pain. All occurred in Pennsaid/DMSO 45.5% treatment arms; no subjects treated with 4.55% DMSO experienced C-V events. This finding may be of concern.
- It is unclear whether adverse events reporting and recording stopped with discontinuation of a study medication for any reason (end of trial or withdrawal for any reason), or continued for some time after that. If the follow-up observation stopped with the stop of a study medication then the number of adverse events that might have occurred shortly after this, would have been missed.

Conclusion:

- The number of cardio-vascular events, including two fatal MI, occurred with the use of Pennsaid/DMSO 45.5%. Potential of either diclofenac or DMSO causing it should be evaluated more closely. Study is required in a larger population with prolonged use.
- Adverse events of diclofenac include GI side effects such a bleeding and perforation. There are a number of withdrawals due to GI side effects among Pennsaid/DMSO 45.5% treated patients. This requires further investigation. Further clarification of the adverse events seen with the use of DMSO 45.5% alone is needed.
- Two cases of discontinuation from the study due to blurred vision need further clarification. There are reports of lens opacities in reviewed literature observed in different animal species with the chromic use of DMSO. There are no adequate chronic use studies in human. Ophthalmologic evaluation should be included in future study.

3. Clinical Laboratory Findings

The following integrated laboratory shift table (Table #5) displays the overall changes in each variable. Each of the studies is represented by both pre-study and post-study display of Pennsaid, Control and Placebo treatment groups.

Table #5: Laboratory Results for Study #102-93-1 and #107-96
(Sponsor's table #8, Item # Application Summary, Clinical Data, electronic Submission)

Lab	PENNSAID®	Control	Placebo	χ^2 or Fisher's Exact	2-tailed Fisher's Exact

Variable	N (%)	N (%)	N (%)	Test (F) - study #107-96	Test - study #102-93-1
Hemoglobin					
Unchanged/Improved	112 (95.73%)	108 (95.58%)	109 (98.20%)	0.494[F]	NS
Normal→Abnormal	5 (4.27%)	5 (4.42%)	2 (1.80%)		
Hematocrit					
Unchanged/Improved	111 (94.87%)	108 (96.43%)	109 (98.20%)	0.306[F]	NS
Normal→Abnormal	6 (5.13%)	4 (3.57%)	2 (1.80%)		
Platelet					
Unchanged/Improved	117 (99.15%)	106 (95.50%)	105 (96.33%)	0.325[F]	.074
Normal→Abnormal	1 (0.85%)	5 (4.50%)	4 (3.67%)		
WBC					
Unchanged/Improved	106 (94.64%)	100 (96.15%)	100 (96.15%)	0.724[F]	NS
Normal→Abnormal	6 (5.36%)	4 (3.85%)	4 (3.85%)		
Lymph					
Unchanged/Improved	110 (95.65%)	105 (93.75%)	104 (95.41%)	0.958[X]	NS
Normal→Abnormal	5 (4.35%)	7 (6.25%)	5 (4.59%)		
Mono					
Unchanged/Improved	109 (94.78%)	110 (97.35%)	105 (96.33%)	0.403[F]	NS
Normal→Abnormal	6 (5.22%)	3 (2.65%)	4 (3.67%)		
Gran					
Unchanged/Improved	111 (96.52%)	107 (95.54%)	106 (98.15%)	0.194[F]	NS
Normal→Abnormal	4 (3.48%)	5 (4.46%)	2 (1.85%)		
Eos					
Unchanged/Improved	109 (93.97%)	112 (99.12%)	105 (96.33%)	0.695[F]	.022
Normal→Abnormal	7 (6.03%)	1 (0.88%)	4 (3.67%)		
Baso					
Unchanged/Improved	114 (98.28%)	112 (100.00%)	106 (98.15%)	0.331[F]	NS
Normal→Abnormal	2 (1.72%)	0 (0.00%)	2 (1.85%)		
Na+					
Unchanged/Improved	117 (100.00%)	107 (96.40%)	108 (98.18%)	0.067[F]	NA
Normal→Abnormal	0 (0.00%)	4 (3.60%)	2 (1.82%)		
K+					
Unchanged/Improved	113 (96.58%)	106 (95.50%)	110 (100.00%)	0.470[F]	NS
Normal→Abnormal	4 (3.42%)	5 (4.50%)	0 (0.00%)		
Cl-					
Unchanged/Improved	116 (99.15%)	106 (94.64%)	106 (96.36%)	0.064[F]	NS
Normal→Abnormal	1 (0.85%)	6 (5.36%)	4 (3.64%)		
Albumin					
Unchanged/Improved	113 (96.58%)	108 (97.30%)	107 (99.07%)	0.543[F]	NS
Normal→Abnormal	4 (3.42%)	3 (2.70%)	1 (0.93%)		

Lab Variable	PENNSAID® N (%)	Control N (%)	Placebo N (%)	χ^2 or Fisher's Exact Test (F) - study #107-96	2-tailed Fisher's Exact Test - study #102-93-1
Protein					
Unchanged/Improved	115 (99.14%)	112 (100.00%)	105 (98.13%)	0.317[F]	NS
Normal→Abnormal	1 (0.86%)	0 (0.00%)	2 (1.87%)		
Glucose					
Unchanged/Improved	89 (91.75%)	83 (96.51%)	84 (93.33%)	0.121[F]	NS
Normal→Abnormal	8 (8.25%)	3 (3.49%)	6 (6.67%)		
Urea					
Unchanged/Improved	102 (89.47%)	103 (92.79%)	103 (95.37%)	0.185[X]	NS
Normal→Abnormal	12 (10.53%)	8 (7.21%)	5 (4.63%)		
Creatinine					
Unchanged/Improved	113 (98.26%)	107 (98.17%)	106 (98.15%)	0.392[F]	NS
Normal→Abnormal	2 (1.74%)	2 (1.83%)	2 (1.85%)		
Uric Acid					
Unchanged/Improved	111 (94.07%)	100 (92.59%)	102 (93.58%)	1.00[F]	NS

Normal→Abnormal	7 (5.93%)	8 (7.41%)	7 (6.42%)		
Bilirubin					
Unchanged/Improved	111 (100.00%)	103 (97.17%)	101 (97.12%)	0.537[F]	NS
Normal→Abnormal	0 (0.00%)	3 (2.83%)	3 (2.88%)		
SGOT					
Unchanged/Improved	113 (96.58%)	107 (98.17%)	109 (99.09%)	0.866[F]	NS
Normal→Abnormal	4 (3.42%)	2 (1.83%)	1 (0.91%)		
SGPT					
Unchanged/Improved	113 (96.58%)	104 (93.69%)	106 (98.15%)	0.031[F]	NS
Normal→Abnormal	4 (3.42%)	7 (6.31%)	2 (1.85%)		
Alk. Phos.					
Unchanged/Improved	117 (99.15%)	105 (95.45%)	109 (99.09%)	0.288[F]	NS
Normal→Abnormal	1 (0.85%)	5 (4.55%)	1 (0.91%)		
U-Protein					
Unchanged/Improved	112 (99.12%)	106 (96.36%)	105 (96.33%)	0.248[F]	NS
Normal→Abnormal	1 (0.88%)	4 (3.64%)	4 (3.67%)		
U-Blood					
Unchanged/Improved	97 (87.39%)	107 (97.27%)	102 (91.89%)	0.228[χ]	.038
Normal→Abnormal	14 (12.61%)	3 (2.73%)	9 (8.11%)		
U-Leuko					
Unchanged/Improved	75 (92.59%)	68 (89.47%)	72 (92.31%)	0.777[χ]	ND
Normal→Abnormal	6 (7.41%)	8 (10.53%)	6 (7.69%)		
U-M:WBC/HPF					
Unchanged/Improved	72 (92.31%)	64 (85.33%)	72 (93.51%)	0.290[χ]	ND
Normal→Abnormal	6 (7.69%)	11 (14.67%)	5 (6.49%)		
U-M:RBC/HPF					
Unchanged/Improved	77 (98.72%)	74 (98.67%)	72 (93.51%)	0.254[F]	ND
Normal→Abnormal	1 (1.28%)	1 (1.33%)	5 (6.49%)		
U-M:Cast (hyaline)					
Unchanged/Improved	78 (98.73%)	74 (98.67%)	75 (97.40%)	0.841[F]	ND
Normal→Abnormal	1 (1.27%)	1 (1.33%)	2 (2.60%)		
U-M:Cast (granular)					
Unchanged/Improved	79 (100.00%)	73 (97.33%)	77 (100.00%)	0.307[F]	ND
Normal→Abnormal	0 (0.00%)	2 (2.67%)	0 (0.00%)		
LDH					
Unchanged/Improved	23 (88.46%)	21 (91.30%)	24 (96.00%)	ND	NS
Normal→Abnormal	3 (11.54%)	2 (8.70%)	1 (4.00%)		

Lab Variable	PENNSAID®		Control		Placebo		χ^2 or Fisher's Exact Test (F) - study #107-96	2-tailed Fisher's Exact Test - study #102-93-1
	N	*(%)*	*N*	*(%)*	*N*	*(%)*		
pH								
Unchanged/Improved	30	(100.00%)	31	(100.00%)	30	(100.00%)	ND	NA
Normal→Abnormal								
U-Glucose								
Unchanged/Improved	32	(96.97%)	34	(100.00%)	30	(96.77%)	ND	NS
Normal→Abnormal	1	(3.03%)	0	(0.00%)	1	(3.23%)		
Spec. Gracity								
Unchanged/Improved	27	(90.00%)	30	(93.75%)	27	(90.00%)	ND	NS
Normal→Abnormal	3	(10.00%)	2	(6.25%)	3	(10.00%)		

*Control-45.5% DMSO; Placeb0-4.55% DMSO

Comments:

- The only laboratory values submitted by the sponsor are for studies #102-93-1 and #107-96.

- For two pivotal studies #109 and #109-US the sponsor did not submit any laboratory data.
- Review of data listing of abnormal laboratory data for trials #107-96 and #102-91 revealed the following:

Table #6: Abnormal laboratory data for trials #107-96 and #102-93-1

Hb 120-160 g/L-(F) 135-170 g/L (M)	**Pennsaid**	**Control-DMSO**	**Placebo**
Pt#4044			
Pt#3041			
Pt#340			
Total:	1(1/125)	2 (2/122)	

b(4)

Glu 3.9-7.8 mmol/L	**Pennsaid**	**Control-DMSO**	**Placebo**
Pt #1014			
Pt #1016			
Pt#1035			
Pt#3030			
Pt#3032			
Pt#4044			
Pt#4052			
Pt#4058			
Pt#5016			
Pt#5017			
#340			
#338			
#344			
Total:	7(7/125)	4(4/122)	2(2/123)

b(4)

SGPT	**Pennsaid**	**Control-DMSO**	**Placebo**
Pt #4040			
Pt#3011			
#348			
#344	22/36 (0-35)		
Total:	2 (2/125)	1(1/122)	1 (1/123)

b(4)

WBC's (4.8-11.0 X10 9/L	**Pennsaid**	**Control-DMSO**	**Placebo**
Pt #4052			
#1043			
#1033			
#1037			
#1065			
#1071			
Pt #4058			
Pt #5016			
Total:	4(4/125)	1(1/122)	1(1/123)

For trial #102-91 some lab tables do not contain WBC's data

b(4)

Plt (145-400 x 10 9/L)	**Pennsaid**	**Control-DMSO**	**Placebo**
#4058			

b(4)

#1065			
Total	1(1/125)	1 (1/122)	

b(4)

Creatinine (50-120)	Pennsaid	Control-DMSO	Placebo
#3032			

Did not find any normal to abnormal. Many missing follow-up measurements

This reviewer's analysis is less complete than the sponsor's table #8 (Item 3, Application Summary, Clinical Data, Electronic Submission). The sponsor did not provide information on how many patients in these two trials did not have follow-up labs, therefore rates are underestimated. The rates presented by the sponsor in the sponsor's table #8 are higher and are of concern.

Conclusions:

- LFT and hematologic abnormalities rates as reported are potentially meaningfully higher in the Pennsaid /DMSO 45.5% treated subjects compare to the 4.55% treated subjects.
- Consistent trend in WBC's decrease (less so with platelets) with both Pennsaid and DMSO 45.5% versus placebo arm may suggest that DMSO has hematologic effects. No definitive statement can be made. Further study is needed.
- This reviewer's analysis of Glucose level raises some concerns as well.
- Summary of lab data derived from trials of 4-6 weeks duration therefore no conclusions can be drawn about long-term safety. The absence of long-term (> 3 months) lab data is of major concern.
- Given the low power to detect statistically significant difference, trends must be the basis for safety assessment. This is particularly true for a drug that includes a component such as DMSO for which there are very little controlled data.

4. Other safety assessments

a. Renal safety

The renal toxicity associated with oral NSAIDs (i.e., decreased renal perfusion, sodium and fluid retention, and decreased renal function) may be caused by inhibition of renal prostaglandins, which are directly involved in the maintenance of intra-renal hemodynamics and sodium and fluid balance. Prostaglandins are particularly important in maintaining renal function in the presence of generalized vasoconstriction or volume depletion. The sponsor states in the application that the amount of diclofenac sodium found in the blood and reaching the kidney following topical administration of Pennsaid is small (127-135 times lower after application of 1 mL of Pennsaid than with administration of standard 50 mg oral dose of diclofenac sodium), and the potential of Pennsaid to cause renal toxicity is significantly reduced.

Several markers of renal toxicity were measured in the phase III studies #102-93-1 and #107-96.

The sponsor states that the urinalysis results revealed an increased number of patients with hematuria in the active group.

Breakdown of blood urea and blood creatinine tests by study

Table #9: Change in Laboratory Analysis Data from Pre-study to Post-Study - Blood Urea and Creatinine Levels - Study #102-93-1 (Sponsor's table #67, Vol 1.59, p. 49)

		PENNSAID® (A)		Control (C)		Placebo (P)	
	pre → post	N	%	N	%	N	%
Urea	N → Ab	3	9.1%	4	11.8%	2	6.3%
Creat.	N → Ab	1	3.2%	0	0%	0	0%

Only 35 patients were exposed to Pennsaid for > 30 days

Table #10: Change in Laboratory Analysis Data from Pre-study to Post-Study - Blood Urea and Creatinine Levels - Study #107-96 (Sponsor's table #68, Vol 1.59, p. 49)

		PENNSAID® (A)		Control (C)		Placebo (P)	
	pre → post	N	%	N	%	N	%
Urea	N → Ab	9	11.4%	4	5.6%	3	4.2%
Creat.	N → Ab	0	0%	2	2.8%	2	2.7%

Only 1 patient was exposed to Pennsaid for > 30 days

Comment:

- typically renal toxicity manifests late in disease course. Labs are insensitive to early damage therefore any signal even in a short study is of great concern.

Conclusions:

- Limited patients' exposure does not allow any definite conclusions
- Diclofenac may affect renal function
- DMSO in reports-extremely limited info available
- Combo of diclofenac/DMSO may be synergistic
- Signal in small, very short-term study suggest that more data is required from studies of longer duration

b. GI safety

Table #11: Total Number of Patients With GI-Related Adverse Events - Study #102-93-1, #107-96, #108-97, RA-CP-109 and RA-CP-109-US

Treatment Group:	**PENNSAID®**		**DMSO 45.5%**		**Placebo**	
Body System Event	N=446 Total		N=442 Total		N=175 Total	
Body As A Whole						
Abdominal Pain	13	(2.91%)	5	(1.13%)	9	(5.14%)
Digestive System						
Diarrhea	4	(0.90%)	6	(1.36%)	4	(2.29%)
Dyspepsia	20	(4.48%)	17	(3.85%)	7	(4.00%)
Eructation	0	(0.00%)	1	(0.23%)	2	(1.14%)

Flatulence	0	(0.00%)	0	(0.00%)	1	(0.57%)
Gastroenteritis	1	(0.22%)	0	(0.00%)	1	(0.57%)
Nausea	8	(1.79%)	9	(2.04%)	3	(1.71%)
Vomiting	0	(0.00%)	1	(0.23%)	1	(0.57%)

Comment:

- The table is misleading because it shows pooled data from several trials of different duration.

Breakdown data for individual trials #107-96+ #102-93-1 combined; #108-97; #109; #109-US, although very limited, show the following:

Table #12: The range of GI-related AEs from different trials

	Pennsaid	DMSO 45.5%	Placebo (only for #107-96; #108-97; #102-93-1)
Abdominal pain	2.44% 3.7% 4%	0.61% 1.62% 2%	4.7%-7.7%
Diarrhea	2.4% 0.9%	1.85% 2.46%	1.9%-2.44%-3.8%
Dyspepsia	2% 5.6% 4.0%	0.9% 4.92% 8.2%	1.9%-4.88%-9.6%
Eructation	none	2%	1.63%
Flatulence	2.44%	1.23%	0.81%-3.8%
Gastroenteritis	0.61% 0.9%	none	0.81%
Nausea	0.9% 4%	0.62% 2% 4.1%	0.81%-3.8%
Vomiting	none reported	none reported	0.81%

Controlled trials #109 and #109-US do not have a Placebo arm (DMSO 4.55%)

Comments:

- Melena was reported in one patient in trial #109 (DMSO 45.5%) and in one patient in trial #109-US (DMSO 45.5%). There were no data provided on how those patients were evaluated and followed-up.
- Dyspepsia, nausea/vomiting, diarrhea, gastritis were reported in a number of patients.

Conclusions:

- As with other diclofenac-containing medications, GI/liver toxicity of Pennsaid cannot be excluded until more data are available.
- Two cases of melena in DMSO 45.5% treated patients raise a concern about potential GI side-effects of DMSO. Without more data no further conclusions can be drawn.
- Synergistic effect of Pennsaid and DMSO cannot be excluded.
- Co-use with other NSAIDs is of major concern.
- Monitoring of LFTs should be indicated especially with chronic use.
- More studies of longer duration are needed to evaluate long-term GI safety of Pennsaid and DMSO.

d. Skin safety

Since Pennsaid is a drug applied to the skin, its potential for localized adverse reactions was evaluated.

A. Analysis of irritation/sensitization studies #100-89; #101-89-2; #103-93-2 and #104-93-3.

Total of four phase I skin irritation/sensitization studies were submitted in support of this NDA: #100-89; #101-89-2; #103-93-2 and #104-93-3 and one phase III study with a subset of patients underwent sensitization testing after the treatment period. Irritation was scored according to a pre-determined scale of 0 to 4, for each of the studies, with a slight variation from study to study.

Almost all studies used diclofenac in a concentration of 1.5 % except for #100-89 study that used diclofenac in a concentration of 10%.

These studies are reviewed and summarized in the dermatological consult.

Comment:

- According to the consult, because a preparation containing diclofenac but without DMSO had not been tested it is impossible to distinguish between irritation and sensitization.
- Deficiencies noted in dermatological review would not preclude approvability; the overall quality of safety data is of concern.

B. Analysis of skin-related adverse events from #102-93-1, #107-96, #108-97, RA-CP-109, RA-CP-109-US (double-blinded, randomized, placebo-controlled trials involving Pennsaid, Control-DMSO and/or Placebo)

In order to understand adverse events related to skin, event rates in each trial must be evaluated.

Table # 7. Pooled data from sponsor's tables #9 through #12 (Vol. 1.59, pp. 73-102) on skin-related adverse events

Adverse event	Pennsaid				Control-DMSO				Placebo	
	107-96; 102-93-1	108-97	109	109-US	107-96; 102-93-1	108-97	109	109US	107-96; 102-93-1	108-97
Paresthesia (application site)	13.6%	30.0%	1.9%		20.49%	18.4%	1.8%		6.5%	19.2%
Dry Skin (application site)	40.8%	70%	38.3 %	32.9%	13.93%	44.9%	21.1%	26.54%	1.63%	19.2%
Pruritus (application site)	7.2%	6%			7.38%	18.4 %	1.8%		3.25%	5.8%
Rash (application site)	12%	16%	1.9%	10.98%	4.92%	8.2%	3.7%	3.7%	3.25%	1.9%
Urticaria (application site)	0.8%				0.82%					

Contact dermatitis			0.9%				0.9%			
Vesicobullous rash	0.8%	2%	0.9%			2.0%	0.9%			
Pustular rash			0.9%							
Maculopapular rash		2%								
Rash		4%	1.9%	2.44%	2.46%		1.8%	1.85%	3.25%	1.9%

Studies #109 and #109-US do not have a Placebo (DMSO 4.55%) arm

Comment:

- The data are not consistent and the range of adverse event differs significantly in different studies. One possible explanation for this is the different studies were of different duration and used different methods of data collection and adverse event ascertainment. It is unclear whether the numbers of adverse events that appeared in the sponsor's tables #9-12 (Vol. 1.59) were derived from patients diaries, investigator CRF entry, formal irritation score assessment or any combination of these three types of assessment.

C. Analysis of skin-related adverse events from uncontrolled studies (EDR and #105-95)

There were no adverse events reported for the EDR.
EDR is Emergency Drug Release Program, that took place in Canada from March 1994 through March 1995 and was replaced by Phase III, non-blinded, non-placebo-controlled, open-labeled study #105-95 (1995-1999). Estimated 244 patients were exposed to Pennsaid in EDR and 2654 patients- in study #105-95.

Table #8. The skin-related adverse reaction rates in open-label study #105-95

Paresthesia	8 (0.30%)
Application skin reaction	33 (1.24%)
Dry skin	11 (0.41%)
Pruritus	9 (0.34%)
Skin discoloration	2 (0.08%)
Skin ulcer	1 (0.04%)
Rash	38 (1.43%)
Vesiculobullous rash	4 (0.15%)
Urticaria at application site	3 (0.11%)

Comment:

- Given the very low reporting rates in this open-label database and consistency of higher rates in controlled trials, underreporting and the quality of data in open-label studies represent a serious concern. Therefore, the safety conclusions must rely on limited number of patients exposed to study medications in controlled clinical trials.

Conclusion:

- In general, it appears that skin-related adverse reactions represent a significant problem with both Pennsaid and DMSO but the long-term safety data derived from two uncontrolled studies are not adequate to fully assess long-term skin-related safety of study medications (both Pennsaid and DMSO)
- If the drug were approved, label should include:
    a. The application area should be clean and dry before application of Pennsaid
    b. Pennsaid should not be applied to open skin wounds, infected areas or areas affected by exfoliative dermatitis
    c. In clinical studies, localized dermal reactions including irritation, rash, pruritis, dry skin, scaling and, on rare occasions, bullous rash and skin erosions, were found in patients treated with Pennsaid with a much higher frequency than in those on placebo.
    d. Patients should understand the importance of monitoring for signs and symptoms of skin adverse reactions. If severe dermal reactions occur, treatment with Pennsaid should be interrupted.
    e. Concomitant exposure to sunlight while using Pennsaid have not been studied.
    f. Safety and efficacy of the use of Pennsaid together with other dermal products have not been studied.

VI. Drug Interaction Studies

Statement by the sponsor says that a formal study of all possible drug interactions with Pennsaid is impractical because the low blood level of diclofenac in the blood of patients using Pennsaid suggests that the likelihood of any such drug interactions is extremely remote.
There were no formal pharmacokinetic and pharmacodynamic studies designed to study drug-drug interactions.

Comments:

- Tables #62, #63 (Vol. 1.59, p. 214-269) list adverse events by therapeutic categories that occurred in patients using concomitant medications. It is difficult to comment because concomitant medications are listed under group name (such as analgesics, allergy therapy, anemia therapy etc). It is not clear whether any particular medication in each group causes more side effects then other medications from the same group.

Conclusion:

- Potential interactions of Pennsaid with oral NSAIDs are of concern and should be evaluated.

VII. Drug Abuse and Overdose Experience

There is no human experience regarding Pennsaid overdosage.
There are two pharmacologically-significant ingredients contained in Pennsaid-diclofenac sodium and dimethyl sulfoxide (DMSO).

The sponsor has submitted data on potential effects of overdose with Pennsaid and DMSO:

"If Pennsaid is abused by topical application:

The mean peak plasma concentration (C_{MAX}) of diclofenac sodium was 11.80 ng/mL after application of 1 mL of PENNSAID® in single-dose pharmacokinetic study (study #106-95). If one assumes that the same ratio of absorption will be maintained if the entire 60 mL bottle is spread over the body, the peak plasma level might be 60 x 11.8 = 708 ng/mL. This is less than the reported diclofenac sodium plasma level of 1.5 μg/mL achieved after the oral consumption of a tablet containing 50 mg of diclofenac sodium".

Comment:

- There is a potential for Pennsaid abuse by topical application. Most people perceive the topical applications as being safe, and might be using the solution on different areas of the body such as shoulder joint, hip joints etc. It is impossible to comment on what is going to happen if someone chronically use the dose of a drug much higher that was prescribed.

"If PENNSAID® is abused by oral ingestion:

The concentration of diclofenac sodium in PENNSAID® is 1.5% w/w or 1.5 g per 100 g. Therefore, a full 60 mL bottle of PENNSAID®, weighing approximately 64.2g will contain 1.5 ÷ 100 x 64.2 = 963 mg of diclofenac sodium. If PENNSAID® is abused by ingestion, the amount of diclofenac sodium contained in one 60 mL bottle of PENNSAID® is substantial (equivalent to an overdose of about 20 50-mg tablets of diclofenac.)

The concentration of DMSO in PENNSAID® is 45.5% w/w and the amount of DMSO in a full bottle of PENNSAID® is 29.2 g. The LD_{50} of DMSO in the dog is greater than 10g/kg. In a typical 60 kg female, the exposure after ingestion of one 60 mL bottle of PENNSAID® would be 0.487 g/kg, less than $^{1}/_{20}^{th}$ of the LD_{50} observed in the dog".

VIII. Post-marketing Experience.

Comments:

- Sponsor did not provide any postmarketing data from foreign market of topical diclofenac.
- The postmarketing adverse events from AERS database were analyzed separately in the review by Claudia B. Karwoski, Pharm.D., Safety Evaluator Team Leader, Division of Drug Risk Evaluation, HFD-430 (See Appendix 2)

IX. Conclusions

The safety database is inadequate. The reported adverse events from the only sources of information beyond 12 weeks have substantially lower reporting rates than that seen in the controlled studies of 12 weeks or less. There are no clinical AEs reported for EDR. The lack of AEs reporting is inconsistent with most controlled trials data submitted with the application. The rates of AEs in study 105-95 are very low compared to the controlled studies even for skin reactions that are very common with the use of this drug. This suggests that these important studies had significant underreporting of events. This makes interpretation of these databases difficult and therefore cannot be viewed as adequate clinical safety data for long-term use of the drug.
The laboratory safety data is limited to approximately 100 patients per treatment arm in studies 102-93-1 and 107-96. The vast majority of exposure was 30 days or less in these studies combined. The pivotal efficacy trials 109 and 109-US did not include laboratory information. Imbalances in adverse event rates cannot be interpreted adequately in very small databases and the potential magnification of signals with longer broader exposure cannot be predicted. Within this limited database there were signals in the 45% DMSO containing arms for potentially significant alterations in hematologic and hepatic parameters as well as serum glucose levels that require further study in a larger database. In addition, there were multiple cardiovascular events in the 45% DMSO containing arms of the trial and none in the placebo (4.5% DMSO) arms. Larger databases will be needed to evaluate this finding. Further clarification of the adverse events seen with the use of DMSO 45% alone is needed.

It is also important to note that there is no safety information on the use of Pennsaid with daily oral anti-inflammatory and analgesic therapies; the latter are likely to be used since topical preparations are only applied to a targeted joint.

APPENDIX #1

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

Tel 301-827-2020
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M E M O R A N D U M

Date: May 16, 2002

From: Hon-Sum Ko, M.D., Medical Officer

Through: Susan Walker, M.D., Dermatology Team Leader and
Jonathan K. Wilkin, M.D., Division Director

To: Lee Simon, M.D., Division Director, HFD-550

Re: Consult 293 (DDDDP#029788) dated 2/8/02 and resent 2/26/02 from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products and assigned 2/15/02. In the Request for Consultation, the box "Safety/Efficacy" under "I. General" has been checked off. The COMMENTS/SPECAIL INSTRUCTIONS box gives:

"Please forward all comments and review to Nancy Halonen, Project Manager, HFD-550 Rm N313, ext. 7-2019

"Since this is the first NSAID topical analgesia/anti-inflammatory that may be approved from HFD-550, we need to be sure that this has a complete and proper review of all aspects of safety and efficacy. We would like the derm consult to help in this effort and hope that part of that will include an assessment and opinion as to whether the types of studies submitted by the sponsor are sufficient towards an NDA approval. In other words, not only are the submitted studies adequate to demonstrate safety but are these studies complete in addressing all the usual aspects of safety that should be considered in this regard."

This consult is on NDA 20-947, PENNSAID (diclofenac sodium 1.5%) Solution from Dimethaid Research, Inc. of Markham, Ontario, Canada, originally submitted 12/15/97, withdrawn 10/26/98, and resubmitted 8/7/01. Due to a major amendment received on 3/29/02, PDUFA goal dates are: 9/8/02 (primary), & 11/8/02 (secondary).

Material Reviewed

NDA 20-947 Volumes 8.11 through 8.14, and the following Electronic files:

- Item 2: Labeling, and
- Item 8: Clinical Data: Sections A.4a (List of INDs), D-E (Table of All Controlled Clinical Studies), and H (Integrated Summary of Safety)

Executive Summary

This NDA presents an NSAID, diclofenac, in a solution containing DMSO (PENNSAID Solution) for the treatment of osteoarthritis.

Five studies have been reviewed in this consult: four phase 1 dermal safety studies and one phase 3 trial on the safety and efficacy of PENNSAID Lotion in the treatment of osteoarthritis, with sensitization testing in a subset of patients after the treatment period. The phase 1 studies examined the potential of PENNSAID Lotion for irritancy, contact sensitization, photoirritation, and photoallergenicity. In each of the five studies, in addition to the PENNSAID Lotion, two other test products were applied: Placebo-H (Placebo-1), which was the vehicle lotion without diclofenac, and Placebo-L (Placebo2), a vehicle containing a low strength of DMSO (1/10 as in PENNSAID or in Placebo-H). The studies were:

Phase 1
100-89. Primary cumulative skin irritation potential of PENNSAID® Topical Lotion
101-89-2. Skin sensitization study of PENNSAID® Topical Lotion
103-93-2. A skin photoirritation potential of PENNSAID® Topical Lotion
104-93-3. A modified Draize photosensitization study of PENNSAID® Topical Lotion
Phase 3
107-96. A double-blinded, placebo-controlled, three-way parallel clinical trial to confirm the safety and efficacy of PENNSAID® treatment and to compare two methods of measuring pain of the osteoarthritic knee

The results of the studies can be summarized in the following Tables. Data from Study 103-93-2 are not shown, as there were no positive reactions in photoirritation testing.

Mean Irritancy Scores in the Induction Phase

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89 (N=23)	0.300 ± 0.764	0.158 ± 0.378	0.051 ± 0.172
	P-values (one-way ANOVA): PENNSAID vs Placebo-1=0.272, PENNSAID vs Placebo-2=0.057, Placebo-1 vs Placebo-2=0.406.		
101-89-2 (N=206)	0.030 ± 0.226	0.009 ± 0.091	0.005 ± 0.077
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.105, PENNSAID vs Placebo-L=0.062, Placebo-H vs Placebo-L=0.805.		
104-93-2 (N=27)	0.042 ± 0.109	0.040 ± 0.123	0.017 ± 0.069
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.873, PENNSAID vs Placebo-L=0.113, Placebo-H vs Placebo-L=0.153.		
107-96	Safety and efficacy study with no induction phase		

Positive Challenge and Rechallenge Rates

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89			
Challenge Rechallenge (% positive)*	4/23 3/6 (13.0%)	6/23 1/4 (4.3%)	2/23 0/3 (0)
101-89-2			
Challenge Rechallenge (% positive)	8/204 5/8 (2.5%)	5/206 3/5 (1.5%)	1/205 0/1 (0)
104-93-3			
Challenge (non-irradiated vs irradiated) Rechallenge (non-irradiated vs irradiated) (% positive)	8/27 vs 7/27 5/8 vs 5/8 (18.5%)	6/27 vs 5/27 3/6 vs 3/5 (11.1%)	2/27 vs 2/27 1/3 vs 1/3 (3.7%)
107-96			
Challenge Rechallenge (% positive)	16/49 12/16 (24.5%)	9/46 7/9 (15.2%)	0/44 0/0 (0)

*% positive is calculated by dividing the number of subjects with positive rechallenge reactions by the total who underwent challenge.

The following Conclusions can be drawn from the material reviewed:

1. The dermal safety studies should be done on the to-be-marketed formulation. As the product proposed for marketing is a "solution", and the studies reviewed used a "lotion", it is unclear whether they represent the same product, even if the compositions are the same. The solubility of the ingredients may affect safety and efficacy, and hence the applicability of the conclusions to be drawn from the studies to the marketing formulation.

2. The dermal safety studies were not conducted under GLP, and the study reports contain internal inconsistencies. The design of the studies appears to be acceptable to obtain the needed information on the potential for dermal toxicity, although the provocation use test (PUT) in these studies is both inadequate and unnecessary. The Applicant has not presented their rationale in conducting photoirritation and photosensitization studies, which could be waived if none of the components of the drug product absorb in the UV-B, UV-A or the visible spectrum. However, it is known that diclofenac does absorb in the UV-B spectrum.

3. Dermal safety studies are usually performed on normal skin at the back or upper extremities in healthy volunteers. Caution should be exercised in the extrapolation of their data to other anatomic regions in specific patient groups. For instance, there was a much higher positive reaction rate in the sensitization testing in the phase 3 trial, 107-96, than in the contact sensitization study, 101-89-2. It is unclear whether differences in the population (older patients and overwhelming Caucasians in 107-96), previous therapies or the disease itself could be factors contributing to these variations.

4. It should be emphasized that contact sensitization testing involves a type IV dermal reaction for delayed hypersensitivity. Immune mechanisms such as anaphylaxis or other antibody-mediated reactions would not be tested by the studies submitted.

5. The data from the four dermal safety studies in this application suggest that PENNSAID Lotion is of low photoirritation and photosensitization potential. However, DMSO is by itself a known irritant, and the data suggest that the presence of diclofenac enhanced irritancy of the product. Interpretation of the sensitization testing data is complicated by the irritancy effect of DMSO and diclofenac (positive rates of 2.5%-18.5% for PENNSAID and 1.5%-11.1% for vehicle). In the phase 3 study, 107-96, the rates were even higher (24.5% for PENNSAID and 15.2% for vehicle). As a preparation containing diclofenac but not DMSO has not been tested, it is not possible to distinguish between irritation and sensitization from these studies. Because of this, the sensitization potential of PENNSAID is not excluded, but not proven.

6. One serious adverse event was reported in the four dermal safety studies (death due to cancer in 101-89-2). Other than skin test reactions, no other adverse events have been noted. Adverse event reporting in these studies appears to be inadequate. In the phase 3 trial, Study 107-96, the adverse events leading to discontinuation that might be related to the use of PENNSAID were rash, pruritus, halitosis and body odor, while desquamation ("dry skin") was observed in more than a third of patients. These risks should be carefully weighed against the benefits.

7. Systemic safety depends on systemic bioavailability, and would be supported by PK data, adverse event reporting, and clinical laboratory testing. The reviewed material does not contain PK information. In the phase 3 trial, Study 107-96, adverse event reporting and lab tests suggest that PENNSAID Lotion was well tolerated in general. Although transaminase elevation was observed in a patient using PENNSAID Lotion, its relationship to treatment is uncertain. Systemic exposure data would be helpful to determine whether the toxicities of oral diclofenac preparations, including liver toxicity, should be seriously considered for PENNSAID Lotion or not.

Introduction

This consult request s (a) an **assessment** and **opinion** as to whether the types of studies are sufficient, and (b) whether the studies are **complete** in addressing all the usual aspects of safety that should be considered towards NDA approval.

PENNSAID® (diclofenac sodium) Topical Solution, 1.5%, in NDA 20-947 has the proposed indication of ——— The unit formula and representative ——— batch formula are: b(4)

Composition of PENNSAID® Topical Solution (1.5% w/w diclofenac sodium, [DMI-F0001- ———			
Ingredients	**mg/g**	**— batch**	**%**
Diclofenac sodium USP	15.0		1.5
Dimethyl Sulfoxide USP	455.0		45.5
Glycerin ———			
Propylene Glycol USP			
Alcohol, ———			
Purified Water USP			
Total Weight of PENNSAID® Topical Solution			100.0

b(4)

Comments

1. The volumes requested for review (8.11-8.14) contain reports on four phase 1 dermal safety studies (100-89, 101-89-2, 103-93-2, 104-93-3) and one phase 3 safety/efficacy study (107-96), which includes testing sensitization in a subset of patients. A ***complete*** *evaluation of* ***all aspects of safety to support an NDA approval*** *is neither possible nor appropriate for this consult. Only the Medical Officer of this NDA has access to all the clinical data and the familiarity with the proposed indication to determine all aspects of safety in conjunction with the product's efficacy for a proper risk-benefit analysis. This consult report will be confined to addressing the dermal safety testing.*

2. The drug product contains 45.5% dimethyl sulfoxide, believed to enhance absorption of diclofenac through the skin. An evaluation of the reported adverse effects of dimethyl sulfoxide solution has been requested of ODS.

3. The drug product is said to be a "solution" in this application. However, in the five clinical studies requested for review, the product tested is said to be a "lotion". As the terminology for the dosage form differs between what has been studied and what is intended for marketing, it is unclear whether the formulations studied and the to-be-marketed product are identical in all aspects, even if the compositions are the same.

The Studies presented for review in this consult are:

Phase 1

100-89. Primary cumulative skin irritation potential of PENNSAID® Topical Lotion
101-89-2. Skin sensitization study of PENNSAID® Topical Lotion
103-93-2. A skin photoirritation potential of PENNSAID® Topical Lotion
104-93-3. A modified Draize photosensitization study of PENNSAID® Topical Lotion

Phase 3

107-96. A double-blinded, placebo-controlled, three-way parallel clinical trial to confirm the safety and efficacy of PENNSAID® treatment and to compare two methods of measuring pain of the osteoarthritic knee

An overview of these studies is given in the following Table:

Protocol # Investigators	Completion Status (Start Date)	Design	Treatment Doses	Age Range (Mean)	M/F B/W/O	Treatment Duration
#100-89 Dr. H.I. Maibach	Complete (May 5, 1994)	Phase 1, Double- Blind, 4-way, Unicentered, Irritation and Sensitization Study.	Induction/Irritation: 0.2 mL of study product under occlusion, daily, Monday to Friday for 21 days Challenge: 0.2 mL of study product under occlusion, one application. Re-Challenge: 0.2 mL of study product under occlusion, one application. Provocative Use: 0.2mL offending preparation, twice daily non-occlusive, to cubital fossa, for 7 days.	25 - 78 (48.2)	13 / 12 0/16/9	Irritation - 21 days Sensitization - 5 - 15 days
#101-89-2 Dr. H.I. Maibach	Complete (February 26, 1996)	Phase 1, Double- Blind, 3-way, Unicentered, Sensitization Study.	Irritation/Induction: 0.2 mL of the 3 study preparations applied under occlusion. Applications repeated using same preparations on same sites, Monday, Wednesday, and Friday for 22 days, total of 9 applications. Challenge: 0.2 mL of each of the study preparations applied once under occlusion to new skin sites. Re-challenge: 0.2 mL of only the offending study preparations to newly randomly-allocated sites on back of subject, under occlusion once. Provocative Use: Twice daily non-occlusive applications of offending study preparation to cubital fossa, for 7 days.	17 - 83 (44.7)	119 / 104 68/91/64	Irritation - 22 days Sensitization - 5 - 16 days
#103-93-2 Dr. H.I. Maibach	Complete (March 28, 1996)	Phase 1, Double-Blind, 24-hour, Unicentered, 3-way, Photoirritation Study.	0.2. mL of each study preparation applied occluded to backs, upper arms or forearms.	23 - 77 (46.9)	13 / 12 0/14/11	24 hours
#104-93-3 Dr. H.I. Maibach	Complete (March 25, 1996)	Phase 1, Double-blind, 3-way, unicentered, photoirritation/ photo-sensitization study.	Photoirritation/Induction Phase: 0.2 mL of 3 study preparations applied under occlusion. Applications repeated 3 times weekly, using same preparations on same sites, (Monday to Wednesday) for 19 days, for total of 9 applications. Challenge: 0.2 mL of study preparations applied once under occlusion to duplicate new skin sites (i.e. 2 sites per lotion). Re-challenge: 0.2 mL of offending preparations applied once under occlusion to duplicate new skin sites (i.e. 2 sites per lotion). Provocative Use: Twice daily non-occlusive applications of offending study preparation to cubital fossa, for 7 days.	25 - 79 (58.5)	16 / 11 0/24/3	Photoirritation - 19 days Photosensitization - 5 - 19 days
#107-96 [redacted]	Complete (January 7, 1997)	Phase 3, Double- Blinded, Placebo Controlled, 3-arm Parallel Clinical Efficacy	Treatment Phase: Subjects topically applied 1 ml of study preparations to 4 sites on knee (i.e. left side, right side, back side and front of knee), unoccluded, 4 times daily, for 4 weeks. Challenge: 10 drops (0.25 ml) applied once under occlusion to subject's forearm or back.	26 - 82 (61.8)	91 / 157 7/229/12	28 days

b(4)

[redacted]		and Safety Trial of OA of the knee. 4 weeks	Re-challenge: 10 drops (0.25 ml) applied once under occlusion to subject's forearm or back. Provocative Use: 10 drops (0.25 ml) applied (unoccluded) to cubital fossa, twice daily, for 7 days.			

b(4)

The dermal safety study reports (100-89, 101-89-2, 103-93-2, 104-93-3) contain the disclaimer that they were not conducted in compliance with Good Clinical Practice (GCP) regulation, but done following "good scientific practices." The report for the phase 3 safety/efficacy study (107-96) does state that it was done in compliance with GCP.

I. STUDY 100-89. PRIMARY CUMULATIVE SKIN IRRITATION POTENTIAL OF PENNSAID® TOPICAL LOTION

Objective: To determine the cumulative skin irritation and skin sensitization potentials of PENNSAID on the skin of healthy human volunteers.

Design: **Double-blind, single-center, 4-way, randomized, intraindividual study for irritation and sensitization in 25 healthy subjects (planned). Randomization was by site on the back of the subjects.**

Comment *A sample size of 25 may be acceptable for irritancy testing, but not for sensitization potential. For testing sensitization potential, a sample size of at least 200 is recommended.*

- Testing Procedures. The study consisted of 3 periods after the initial screening visit to determine eligibility

and obtain informed consent. In the **Irritation/Induction Phase** (Day 1-22), each subject received 0.2 mL application of each test drug (total of 4; see below) to the back with an occlusive system of a polypropylene chamber covered with paper or *Scanpor* tape (a patch) for 24 hours. The patch was removed the next day, followed by evaluation of the site and scoring. The same patches were repeated on the same sites daily (except for weekends, when they stayed for 72 hours) for 21 days, with a total of 15 applications and 15 evaluations. A 10-day **Rest Phase** ensued before challenge, potential rechallenge and provocative use tests (PUT). In the **Sensitization Test Phase**, each subject is ***challenged*** with reapplication of the test drugs over 4 new sites on the back, with patches in place for 48 hours, and evaluation at patch removal as well as 96 hours from the beginning of application. A test score of ≥1 would result in ***rechallenge*** with an identical procedure, whereas a test score of ≥1 at rechallenge would lead to the ***PUT***, which involved non-occlusive application of 0.2mL of test product twice daily for 7 days and evaluation on the 8th day. The report concedes that PUT was also performed in some subjects with a score of 0.5. If a skin score of ≥2 was observed, the skin site would be withdrawn from the study, and a score of 4 would be arbitrarily imputed for all remaining days of evaluation.

The composition of the test products is shown in the following Table:

	Composition of Test Products (% w/w)			
Ingredients	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Diclofenac sodium	1.5	0	0	10.0
Dimethyl Sulfoxide	45.5	45.5	4.55	45.5
Ethanol,				
Glycerin				
Propylene Glycol				
Purified Water				

b(4)

The rationale given in the report for Placebo-2 having a low concentration of DMSO is that its odor ensured blinding. A control with 10% diclofenac sodium was for "dose-ranging" for safety.

- Selection Criteria. Males or non-pregnant females, age ≥18 and in good general health, who signed informed

consent. The following were exclusion criteria:

1. Significant skin disease such as acne, psoriasis or dermatitis
2. Participation in patch test panel within 30 days of study initiation
3. Use of topical or chronic systemic medications, including antihistamines and steroids
4. Dark skin (at Investigator's discretion) if deemed to interfere with grading
5. Allergy to diclofenac, aspirin or other NSAIDS

- Skin Evaluation. Scoring for the skin reactions used the following scale:

0	no visible reaction (negative)
0.5	equivocal response
1	erythema
2	erythema and induration
3	erythema, induration and vesicles
4	bullae

A positive skin sensitization reaction was determined by the development of erythema or worse (score ≥1) at the cubital fossa on the 8th day of PUT.

Results:

The study was conducted 5/5/94 to 6/21/94.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 25 ***subjects*** and 23 completed, 2 failed to come back for

scheduled appointment during Irritation/Induction Phase (ID#s 13 and 25). For Sensitization Testing Phase, all 23 remaining subjects completed. Completion and discontinuation at ***application sites*** occurred as follows:

	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Completion	22	22	23	18*
Discontinuation	1	1	0	5*

*Since there were 7 subjects with discontinuation of application at the CONTROL site shown in subsequent Tables, (with actual Subject IDs), completion of application of the CONTROL test product could have occurred in only 16 subjects.

The subjects included 13 males and 12 females, and age ranged between 25 to 78 (mean 48). There were 16 Caucasians and 9 Hispanics.

- Irritancy Scoring:

Number of Subjects with Positive Scores in Irritation/Induction Phase (Total 23 Completers)

Worst Irritation Scores	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
0.5	4	4	1	2
1	3	1	1	0
2	0	0	0	1
3	0	0	0	0
4*	1	1	0	7

*As per protocol, a score of ≥2 required discontinuation at the test site and imputation of 4 for the rest of the study in that subject. The report also states that none had a real score of 4 showing bullae.

Comment *The above Table is based on Table 18 in the report (vol 8.11, page 180). However, in Table 20 (vol 8.11, page 182), which provides a subset analysis, PENNSAID sites showed 4 males and 2 females having had a score of 1 (3 subjects in Table 18). Such discrepancy needs to be clarified.*

The report has not presented a cumulative irritancy score for each test product. A comparison of the mean scores between PENNSAID and the Placebos was made.

	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Mean Scores ± SD	0.300 ± 0.764	0.158 ± 0.378	0.051 ± 0.172	Not Done

P-values (one-way ANOVA): PENNSAID vs Placebo-1=0.272, PENNSAID vs Placebo-2=0.057, Placebo-1 vs Placebo-2=0.406.

- Sensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Challenge	4/23	6/23	2/23	9/23
Rechallenge	3/6	1/4	0/3	3/9
PUT	0/4	0/2	0/0	0/3

Comments

1. The report states that despite being part of the protocol, there was no mention of rechallenge or PUT performed in the Sensitization Testing Phase (vol 8.11, page 161). However, the report also concedes that contrary to protocol, PUT was performed in some subjects with a score of 0.5 (vol 8.1, page 157). The section "Brief Summary of Adverse Events" agrees with the data in the above Table: "No subject (0.0%) had a positive formal skin sensitization assessment result after completing the PUT" (vol 8.11, page 170). Thus, there is contradictory information regarding the performance of rechallenge and PUT.

2. It is also stated that records of dropouts were **not** kept in the CRFs.

3. There were more subjects undergoing rechallenge than positive challenges (6 rechallenges with PENNSAID despite 4 positive challenges; 3 rechallenges with Placebo-2 despite 2 positive challenges). As well, there were more undergoing PUT than positive rechallenges (4 PUTs with PENNSAID despite 3 positive rechallenge; 2 PUTs with Placebo-1 despite 1 positive rechallenge). Since only scores of ≥1 led to rechallenge or PUT, there should always be fewer rechallenges and PUTs than positive challenges and positive rechallenges, respectively. A reverse finding suggests that in violation of the protocol, some subjects with negative scores went on to the next level of testing.

- Other Adverse Event Information: There were no deaths reported. Besides skin testing reactions and

discontinuation due to the reactions, this report claims that there were no adverse events reported.

Comment *It is unusual that there were no adverse events other than the skin test reactions in a study of 25 subjects lasting for almost 7 weeks. There is a possibility of under-reporting.*

Conclusions:

The study report states:

> "Therefore, it can be seen that upon exposure to PENNSAID™ in this study, only 1 (4%) of 25 subjects required withdrawal due to adverse events, i.e., erythema and induration. This is the same as the number of subjects withdrawn from the Placebo-1 group. In light of this, it can be seen that PENNSAID™ is no more irritating than placebo. Also, throughout this study, only minor skin irritation was reported in subjects tested with PENNSAID ™, again, not significantly greater than placebo.
>
> "Further, no subject (0 (0.0%)) had a positive formal skin sensitization assessment result after completing the full sensitization testing."

Comments

1. The irritancy data appear to be similar between PENNSAID and Placebo-1, which is the vehicle minus diclofenac.
2. A small sensitization study with negative result from 23 subjects gives 95% confidence that the risk of sensitization is no higher than approximately 13%. Generally a larger sample size is needed for testing sensitization. The Applicant has conducted Study 101-89-2 to address this (see below).
3. Use of PUT data to define sensitization potential is not generally considered appropriate. In such testing, maximal provocation should be used to bring out the real potential of the product. The challenge and rechallenge data indicate that PENNSAID as well as the "control" with 10% diclofenac both gave positive reaction (challenge confirmed by rechallenge) in 3 out of 23 subjects, a rate of 13%. This needs to be confirmed with the larger sample size study, 101-89-2.

II. STUDY 101-89-2. SKIN SENSITIZATION STUDY OF PENNSAID® TOPICAL LOTION

Objective: To determine the cumulative skin irritation and skin sensitization potentials of PENNSAID on the skin of healthy human volunteers.

Design: **Double-blind, single-center, 3-way, randomized, intraindividual study for irritation and sensitization in approximately 200 healthy subjects. Randomization was by site on the back of the subjects. The overall design is almost the same as that of 100-89. The following are key differences:**

- This was a larger study with 200 healthy subjects planned (25 for 100-89).
- Only three of the four products used in 100-89 were tested. The "control" with high diclofenac concentration (10%) was removed. Placebos used in 101-89-2 were the same as those in 100-89, but termed differently: Placebo-H and Placebo-L (Placebo-1 and Placebo-2, respectively, in 100-89). Placebo-H is the vehicle of the PENNSAID product, while Placebo-L contains a reduced concentration of DMSO (4.55%, 1/10 the concentration in Placebo-H).

- The Irritation/Induction Phase in 101-89-2 consisted of 9 applications of 48 to 72 hours (week days 48, weekends 72), whereas in 100-89, it was with 15 daily applications of 24 hours (except weekends: 72 hours).
- The Rest Phase was 13 days in 101-89-2 (10 days in 100-89).
- Rechallenge evaluation for 101-89-2 was at 72 and 96 hours from time of patch application, due to the 48th hour falling on a Sunday. In 100-89, evaluation started at the 48th hour, upon patch removal.
- Added exclusion criteria in 101-89-2: females without negative pregnancy test or not using reliable contraception (such as tubal ligation, oral contraceptive, IUD, etc), history of renal, liver or peptic ulcer disorders, and nursing mothers. Females in 101-89-2 had to be postmenopausal for ≥1 year, be surgically sterile, or else practice an acceptable form of birth control, upon having normal menstrual period within 5 weeks, and negative pregnancy test within 1 week of product application.
- Test sites could be permanently discontinued from further application of patches if a skin score of ≥3 was attained (≥2 in 100-89).

Comments

1. A sample size of at least 200 subjects is appropriate.

2. The protocol states discontinuing application when a skin score of ≥2 was attained (vol 8.12, page 84). However, in the actual report, this cutoff became ≥3 (vol 8.12, page 32). As well, the report states that there were 9 applications in the Irritation/Induction Phase (vol 8.12, page 26) while the protocol required 10 applications over 22 days (vol 8.12, pages 84, 86 and 95) There does not seem to be documentation of protocol amendments addressing these changes. It is unclear which cutoff was actually followed in the study.

Results:

The study was conducted 2/26/96 to 4/16/96.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 223 ***subjects*** and 206 completed Irritation/Induction Phase,

17 failed to come back for scheduled appointment during this Phase. One subject discontinued after completion of the Irritation/Induction Phase for having "contracted cancer". For Sensitization Testing Phase, 204 of the 205 remaining subjects entered and completed (Subject #176 did not continue into this phase). Completion and discontinuation at ***application sites*** occurred as follows:

	PENNSAID	PLACEBO-H	PLACEBO-L
Completion	204	205	205
Discontinuation	19	18	18
• Poor tolerance	• 2	• 1	• 1
• Failure to return	• 17	• 17	• 17

The subjects included 119 males and 104 females, and age ranged between 17 to 83 (mean 45). There were 91 Caucasians, 68 Blacks, 53 Hispanics, 5 "Orientals", 5 "Asians" and 1 "NR".

- Irritancy Scoring:

Number of Subjects with Positive Scores in Irritation/Induction Phase (Total 206 Completers)

Worst Irritation Scores	PENNSAID	PLACEBO-H	PLACEBO-L
0.5	5	2	0
1	2	0	0
2	0	0	0
3	0	0	0
4*	2	1	1

*As per protocol, a score of ≥2 required discontinuation at the test site and imputation of 4 for the rest of the study in that subject. As stated above, the study report mentions discontinuing with a score of ≥3, and it is unclear which was followed. The report also states that none had a real score of 4 showing bullae.

Comment *The above Table is based on Table 18 in the report (vol 8.12, page 63). However, similar to the report on 100-89, such data are not consistent with those in Table 20 (vol 8.12, page 65), which would give the number of subjects showing a score of 0.5 with PENNSAID as 6, and a score of 1 with PENNSAID as 5.*

The report has not presented a cumulative irritancy score for each test product. A comparison of the mean scores between PENNSAID and the Placebos was made.

	PENNSAID	PLACEBO-H	PLACEBO-L
Mean Scores ± SD	0.030 ± 0.226	0.009 ± 0.091	0.005 ± 0.077

P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.105, PENNSAID vs Placebo-L=0.062, Placebo-H vs Placebo-L=0.805.

- Sensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID	PLACEBO-H	PLACEBO-L
Challenge	8/204	5/206	1/205
Rechallenge	5/8	3/5	0/1
PUT	2/5	0/3	0/0

- Other Adverse Event Information: One case of death due to cancer was reported. This subject (#103) was a

45-year-old male Caucasian, who completed the Irritation/Induction Phase. The CRF has no details on the cancer or death. It is noted that the reasons for dropout in this subject are internally not consistent in the CRF. In one place, (vol 8.12, page 213E), the dropout is stated to be for "personal reason". In the "Adverse Drug Reaction Form", the discontinuation is due to:

"Patient contracted cancer and could not continue, died."

The date for the adverse reaction has been crossed out and replaced with "dropout 3-25-96" and the description was "Cancer - leading to death".

Besides skin testing reactions and discontinuation due to the reactions, this report claims that there were no adverse events reported.

Comments

1. It appears unusual that Subject #103 could complete the Irritation/Induction Phase and died of cancer before the Sensitization Testing Phase. It is more likely that Subject #103 discontinued due to serious adverse event (cancer), rather than death during the study period. The circumstances surrounding this adverse event are not clear, and it is important that the Applicant provide more details.

2. It is also unusual that there were no adverse events other than the skin test reactions in a study of 223 subjects lasting for almost 7 weeks. There is a possibility of under-reporting.

Conclusions:

The study report states:

> "Therefore, it can be seen that upon exposure to PENNSAID™ in this study, only 1 (4%) of 25 subjects required withdrawal due to adverse events, i.e., erythema and induration. This is the same as the number of subjects withdrawn from the Placebo-H group. In light of this, it can be seen that PENNSAID™ is no more irritating than placebo. Also, throughout this study, only minor skin irritation was reported in subjects tested with PENNSAID™, again, not significantly greater than placebo.
>
> "Two subjects (2 (0.98%)) had a positive formal skin sensitization assessment result after completing the full sensitization testing."

Comments

1. The conclusion that 1 (4%) of 25 subjects exposed to PENNSAID withdrew due to adverse events, i.e. erythema and induration, is not supported by the data in this study. It appears to be an error due to copying from the conclusion for the Clinical Study Report for Protocol 100-89. The data do suggest that PENNSAID is somewhat greater in irritancy potential than its vehicle (PENNSAID: 7 subjects with score of ≤1 and 2 discontinuations due to score of ≥2; Placebo-H: 2 with score of 0.5 and 1 discontinuation due to score of ≥2)

2. Use of PUT data to define sensitization potential is not generally considered appropriate. In such testing, maximal provocation should be used to bring out the real potential of the product. The challenge and rechallenge data indicate that both PENNSAID and the vehicle containing DMSO, "Placebo-H", gave positive sensitization reactions (challenge confirmed by rechallenge): 5/204 (2.45%) for PENNSAID and 3/206 (1.46%) for vehicle. These low rates suggest low sensitization potential of PENNSAID, but above that of its vehicle containing 45.5% DMSO.

III. STUDY 103-93-2. A SKIN PHOTOIRRITATION POTENTIAL OF PENNSAID® TOPICAL LOTION

Objective: To determine the photoirritation potentials of PENNSAID on healthy human skin.

Design: **Double-blind, single-center, 3-way, randomized, intraindividual study for photoirritation in 25 healthy subjects (planned).**

The study consisted of a **Pre-Treatment Screening Visit** and the **Photoirritation Testing**. At the screening, the subjects gave informed consent and underwent inclusion/exclusion interview and medical assessment. The subject's MED (minimal erythema dose) was determined by irradiation of 3 skin sites with different doses of unfiltered light from an air-cooled Kromayer lamp (UV-A and UV-B).

- Testing Procedures. Randomization of test products for application was by site. All subjects were treated

with PENNSAID, Placebo-H and Placebo-L (see Protocol 101-89-2). Before application, the skin was stripped with cellophane tape until it glistened. Then 0.2 mL of test product was applied to the back, upper arm or forearm and left to dry for 10 minutes. Irradiation was then done with a Woods Light Inspecto Lamp (non-erythematous UV-A light of 320-450 nm) for 45 minutes at a distance of 9 inches. The sites were then exposed to 2/3 of an MED from an air-colled Kronmayer Lamp that gives both non-erythematous and erythematous light (UV-B of 285-350 nm). These sites were occluded for 24 hours and then examined for acute photoirritation. The skin reaction was graded with a scale used in Protocols 100-89 and 101-89-2 by a blinded evaluator.

Comments

1. The Applicant has not presented a rationale in conducting photoirritation and photosensitization studies. If there is no absorption in the UV-B, UV-A or visible spectrum by any ingredient of the drug product, these tests would not be necessary.
2. The amount of energy used to determine MED and administered from the Woods Light Inspecto Lamp has not been presented in the protocol or the study report.
3. It is unclear whether the test sites were actually unoccluded or occluded for 24 hours. The protocol requires occlusion (vol 8.13, pages 8 and 20). The report states that there was a protocol deviation and the sites were not occluded (vol 8.12, page 251). Yet, there are other places that mention occlusion. To be even more confusing, within the same Table (Table #5, vol 8.12, page 242), there is conflicting information: "unoccluded" under "Dosing Schedule" and under "Route and Mode of Administration" for Placebo-L, whereas for PENNSAID and Placebo-H, "Route and Mode of Administration" was "occluded".
4. There is no mention of non-irradiated controls for comparison in case the tests were positive.
5. The use of celluphane stripping for photoirritation testing is not conventional. No rationale has been offered. Stripping may be used to potentiate the effect of photoirritation. However, for a 24-hour application, there is the possibility of reduced skin exposure due to enhanced systemic absorption after the stripping.
6. A sample size of 25 is acceptable.

- Selection Criteria. These were virtually identical to those of Protocol 101-89-2, except that the requirement

for normal menstrual period within 35 days of product application was not in Protocol 103-93-2.

- Skin Evaluation. Scoring for the skin reactions used the following scale:

0	no visible reaction (negative)
0.5	equivocal response
1	erythema
2	erythema and induration
3	erythema, induration and vesicles
4	erythema, induration and bullae

Results:

The study was conducted 3/28/96 to 3/29/96.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 25 ***subjects*** and all completed study. The subjects included 13 males and 12 females, and age ranged between 23 to 77 (mean 47). There were 14 Caucasians, 9 Hispanics, 1 "Oriental", and 1 "Indian".

- Photoirritaion Scoring: No positive reactions were observed in any subject for any test product.

- Other Adverse Event Information: This report claims that there were no adverse events reported.

Comment *It may not be unusual that there were no adverse events in a 24-hour study.*

Conclusion:

The study report states:

> "Therefore, there is no risk of photoirritation with the use of PENSSAID™."

Comment *The conclusion of no risk is not warranted. A small study with negative result from 25 subjects gives 95% confidence that the risk of photoirritation is no higher than approximately 12%.*

IV. STUDY 104-93-3. A MODIFIED DRAIZE PHOTOSENSITIZATION STUDY OF PENNSAID® TOPICAL LOTION

Objective: To determine the cumulative skin photoirritation and photosensitization potentials of PENNSAID on the skin of healthy human volunteers.

Design: Double-blind, single-center, 3-way, randomized, intraindividual study for photoirritation and photosensitization in a minimum of 25 healthy subjects.

- Testing Procedures. The study consisted of a **Pre-Treatment Screening Visit, Photoirritation/Induction Phase**, and the **Photosensitization Testing Phase**. At the screening, the subjects gave informed consent and underwent inclusion/exclusion interview and medical assessment. All subjects were treated with PENNSAID, Placebo-H and Placebo-L (see Protocol 101-89-2). However, the terms Placebo-1 and Placebo-2 were also used interchangeably with Placebo-H and Placebo-L, respectively.

The Photoirritation/Induction Phase (Days 1-19) followed screening immediately. The subject's MED (minimal erythema dose) was determined by irradiation of 3 skin sites with different doses of unfiltered light from an air-cooled Kromayer lamp (UV-A and UV-B). After determining MED, during the first treatment visit (Day 1, Monday), 0.2 mL of each test product was applied to the back using an occlusive system of a polypropylene chamber covered with *Scanpor* tape (a patch), to be left for 24 hours. The randomization was by application site. On the second day, the subject returns for patch removal and scoring. The sites were then irradiated with 1 MED of unfiltered light from an air-cooled Kromayer light (UV-A and UV-B light) followed by irradiation with 10 MEDs of window glass filtered non-erythematous light (UV-A). Another patch with the same product was applied to the same site for each of the sites. These procedures were repeated on the third day. On the fourth day, the sites were evaluated and irradiated without patch removal. The fifth day involved repeat evaluation and leaving the patches in place over the weekend. The same procedures were repeated in the second and third weeks, for a total of 9 applications and 14 evaluations.

The Photosensitization Testing Phase (Days 29-47) occurred after a 9-day rest period with no applications or evaluations (Day 20-28). Challenge (Days 29-33) started with application of 0.2 mL of study product under occlusion to new duplicate skin sites. After 24 hours, the patch on the right was removed, and the site evaluated and irradiated with 2/3 MED from a Kronmayer lamp (UV-A and UV-B light) followed by 10 MEDs of window glass-filtered light. This site was left uncovered. The patch on the left side was removed after an additional 48 hours, and then both right and left patch sites evaluated. They were again evaluated after another 24 hours (Day 33). If there was persistent erythema (score of ≥1), rechallenge (Days 36-40) took place at new sites with the same procedure for the offending product, after two days of rest (Days 34-35). Positive finding (score of ≥1; sometimes ≥0.5) would lead to PUT (Days 40-47), which consisted of non-occlusive application of 0.2 mL of study product to cubital fossa twice daily for 7 days and evaluation on the 8th day.

Comments

1. The Applicant has not presented a rationale in conducting photoirritation and photosensitization studies. If there is no absorption in the UV-B, UV-A or visible spectrum by any ingredient of the drug product, these tests would not be necessary.
2. The Photoirritation/Induction Phase did not include non-irradiated controls. This may make interpretation of positive photoirritation reactions difficult.

3. The sample size of 25 minimum is low but consistent with common practice. A larger sample size would be more desirable, as this would give a better risk estimate.
4. Use of both UV-B and UV-A in testing is appropriate. However, using PUT data to define photosensitization potential is not generally considered appropriate. In such testing, maximal provocation should be used to bring out the real potential of the product.

- Selection Criteria. These were the same as those of Protocol 101-89-2.

- Skin Evaluation. Scoring for the skin reactions used almost the same scale as that in Protocol 103-93-2, with

the addition of a letter grade "G", which stands for minimal glazing, such as in the "peau d'orange". However, the report also concedes that "this was not used as a score."

Results:

The study was conducted 3/25/96 to 5/10/96.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 27 ***subjects*** and all completed the study, except that

rechallenge was not completed for subject #27 due to an error of the site administration.

The subjects included 16 males and 11 females, and age ranged between 25 to 79 (mean 59). There were 24 Caucasians and 3 Hispanics.

- Photoirritancy Scoring:

Number of Subjects with Positive Scores in Photoirritation/Induction Phase (Total 27 Completers)

Worst Irritation Scores	PENNSAID	PLACEBO-H	PLACEBO-L
0.5	4	5	3
1	2	0	0
2	0	0	0
3	0	0	0
4	0	0	0

The findings presented in this Table (given in Table #18 and in the Synopsis) are not consistent with those in Table #19, which provides subset breakdown with age and sex. From Table 19, the number of subjects giving a score of 0.5 was 2 for PENNSAID, 2 for Placebo-H and 1 for Placebo-L; there was only one subject with a score of 1 (PENNSAID).

A comparison of the mean scores between PENNSAID and the Placebos was made in the report:

	PENNSAID	PLACEBO-H	PLACEBO-L
Mean Scores ± SD	0.042 ± 0.109	0.040 ± 0.123	0.017 ± 0.069

P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.873, PENNSAID vs Placebo-L=0.113, Placebo-H vs Placebo-L=0.153.

- Photosensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID	PLACEBO-H	PLACEBO-L
Challenge (non-irradiated) Challenge (irradiated)	8/27 7/27	6/27 5/27	2/27 2/27
Rechallenge (non-irradiated) Rechallenge (irradiated)	5/8 5/8	3/6 3/5	1/3 1/3
PUT	0/6	0/4	0/2

Comments

1. In the rechallenge for PENNSAID, Subject #13 gave both positive and negative results at the irradiated site (Table #20, vol 8.13, page 164). This must be an error.
2. The data indicate that the rates of positive reactions at the irradiated and non-irradiated sites were similar, both for the challenge and for the rechallenge tests. The most likely explanation is that these were not photosensitization reactions, but rather evidence of sensitization. These data would have made PUT unnecessary. Moreover, use of PUT data is not generally considered appropriate, as maximal provocation is used to bring out the real potential of the product. In this case, more intense testing has not established the photosensitization potential of PENNSAID.
3. The Investigator had performed rechallenges in some situations without a prior positive challenge. These extra rechallenges were due to positive reactions on the non-irradiated challenge sites, and were thus attempts to clarify their meaning. In one instance (Subject #2 with PENNSAID), the rechallenge turned out to be negative, and in another (Subject #22 with Placebo-L), rechallenge gave positive result and led to PUT.

- Other Adverse Event Information: Besides skin testing reactions, this report claims that there were no

adverse events reported.

Comment *It is unusual that there were no adverse events other than the skin test reactions in a study of 27 subjects lasting for almost 7 weeks. There is a possibility of under-reporting.*

Conclusions:

The study report states:

> "The skin photoirritation and sensitization/photosensitization potentials of PENNSAID™ were demonstrated to be minimal. ..... Throughout this study, only minor skin irritation was reported in subjects tested with PENNSAID™, not significantly greater than placebo. ..... the minor skin

photoirritation and sensitization/photosensitization of PENNSAID™ seems to be an acceptable, low –level risk."

Comments

1. The data indicate that the rates of positive reactions at the irradiated and non-irradiated sites were similar, both for the challenge and for the rechallenge tests. Even without PUT, the more intense testing with occluded challenge and rechallenge has not established the photosensitization potential of PENNSAID. The data are consistent with sensitization rather than photosensitization. However, the rates observed in this study are higher than those seen in 101-89-2: 5/27 (18.52%) for PENNSAID and 3/27 (11.11%) for vehicle (2.45% and 1.46%, respectively, in 101-89-2).

2. A small photosensitization study with negative result from 27 subjects gives 95% confidence that the risk is no higher than approximately 11%.

V. STUDY 107-96. A DOUBLE-BLINDED, PLACEBO-CONTROLLED, THREE-WAY PARALLEL CLINICAL TRIAL TO CONFIRM THE SAFETY AND EFFICACY OF PENNSAID® TREATMENT AND TO COMPARE TWO METHODS OF MEASURING PAIN OF THE OSTEOARTHRITIC KNEE

This is a safety/efficacy study and the study report involves 8 volumes of the submission (vol 8.14 to 8.21), but only vol 8.14 is provided for consultation. The other volumes, which include the references and all appendices, are not part of this review. The protocol and amendments are within the appendices. This consult focuses on the dermal safety data in this study and the sensitization testing.

Objective: To confirm the safety and efficacy of PENNSAID™ in the symptomatic treatment of osteoarthritis of the knee (primary) and to validate the accuracy of Dimethaid's method used to measure osteoarthritic knee pain in clinical trial (secondary)

Comment *The testing for sensitization is not an explicitly stated objective of this study.*

Design: Double-blind, multi-center, 3-arm, randomized, parallel-group study of 150 subjects (planned) with 3 phases: screening visit, treatment phase and sensitization testing phase.

- Study Procedures.

Screening. Patients with suspected osteoarthrits were screened, gave informed consent and underwent inclusion/exclusion interview, medical assessment and knee x-ray (if not taken in last 6 months). Blood and urine were submitted to a pre-designated laboratory for analysis. Patients meeting all entry criteria went through a washout period for narcotic analgesics, oral NSAIDs and other topical arthritic products and related pain-management products for one week. Use of acetaminophen (650 mg four times a day as needed) was allowed, except during the 24 hours prior to baseline WOMAC (Western Ontario MacMaster osteoarthritis questionnaire) assessment.

Treatment Phase (Visit 1 to Visit 5). During this phase, patients were treated as randomized. They were randomized to PENNSAID, "Control" or "Placebo" Each patient was given a bottle of study lotion and instructions for application, using 1 mL (40 drops) per knee four times a day. The use of acetaminophen tablets (325 mg) up to 12 tablets per day was allowed. Starting from Visit 2, signs of skin irritation and the degree of irritation were recorded. Blood and urine sampling were repeated at Visit 5, the final treatment phase visit.

Comment *The compositions of the "Control" and "Placebo" in this study are the same as those of the "Placebo-1" and "Placebo-2", respectively, in Protocol 100-89, and of "Placebo-H" and "Placebo-L", respectively, in Protocols 101-89-2 and 103-93-2.*

Sensitization Testing Phase. For the first 145 patients completing Visit 5, skin sensitization testing was conducted 2 to 4 weeks after the end of treatment, based on the procedures of "challenge", "rechallenge" and "PUT" in Protocol 101-89-2. Challenge was with 10 drops (0.25 mL) of the patient's study lotion on a cotton plug in a plastic chamber, inverting the chamber and taping it to skin (forearm or back) for 48 hours. The Investigator would phone the patient to remove the chamber and describe the degree of irritation observed. After another 48 hours, the patient returned for final evaluation of irritation. If the test site showed erythema (score of ≥1), rechallenge with the same procedure was carried out at a new site. If after 96 hours, erythema was also observed, the patient underwent PUT, which involved non-occlusive application of 10 drops of study lotion to cubital fossa twice a day for one week. A positive sensitization response was defined by a score of ≥1 (erythema) after one week of such application.

Comment *In this study, there was no proper induction phase, and the treatment phase acted for the induction phase of a formal testing. As well, use of PUT data to define sensitization is not generally considered appropriate, and maximal provocation is usually used to bring out the real potential of the product. Thus, the design of this study was not adequate to determine sensitization. However, if positive reactions develop with challenge and rechallenge despite suboptimal induction, the data could be supportive of sensitization observed in healthy subjects in the phase 1 studies.*

- Selection Criteria. Patient with osteoarthritis fitting certain radiologic and clinical criteria were enrolled if

between the ages of 18 and 80 and in reasonably good health, having blood and urine test results within acceptable ranges at screening. Females had to be (a) surgically sterile or postmenopausal for at least 1 year, or (b) not pregnant (normal menstrual period within 35 days of entry and negative pregnancy test within 48 hours of entry), and using acceptable contraception, including oral contraceptives, IUD, spermicide with barrier method, or surgically sterile male partner). Exclusion criteria were:

1. known hypersensitivity or contraindications to the use of diclofenac, DMSO, glycerine, propylene glycol, alcohol, ASA or other NSAID
2. clinically active renal, liver or peptic ulcer disease
3. history of alcohol or drug abuse within 1 year of entry

4. lactation
5. psoriasis (at site of application), syphilitic neuropathy, ochronosis, metabolic bone disease (except osteoporosis or Paget's disease of other than the affected knee) or acute trauma
6. requirement for oral corticosteroids, having received intraarticular steroid injection within 60 days of entry or requiring topical corticosteroid at the site of application

Additional entry requirements included:

- selection consistent with all warnings, precautions and contraindications in the label for oral diclofenac
- discontinued ≥1 week before entry: (a) all oral NSAIDs including OTC ASA and ibuprofen (acetaminophen allowed until 24 hours before first treatment visit), (b) topical products including methyl salicylate, camphor, menthol, capsicum, and OTC analgesics, and (c) glucosamine

• Evaluation Criteria. The evaluations for efficacy will not be addressed in this consult. Safety evaluation included information from patient diary and case report form's adverse event reporting. The study coordinator asked about specific adverse events from a checklist, and offered a subjective opinion whether an adverse event has occurred. ***An event was not considered to be related to application of the lotion if the event occurred in a similar number of patients in each treatment group.*** Events considered related to study drug application included those that occurred at the site of application and events related to the characteristic garlic odor associated with the use of DMSO.

Skin irritation scoring was according to the following scale:

0	no visible reaction or equivocal response (questionable reaction)
0.5	itching sensation
1	erythema (redness)
2	erythema with induration (i.e., swelling)
3	erythema with induration and vesiculation (small blisters <5 mm)
4	erythema with induration and bullae (large blisters > 5 mm)

The criterion for sensitization was the development of erythema (score of ≥1) at the end of PUT.

Comment *The definition of "relatedness" of an adverse event to study drug involves a post-hoc examination of whether the number of cases in the treatment group stands out. This is in contrast to a determination by the Investigator with considerations based on his/her experience and the pharmacology of the drug. Thus, caution should be exercised in interpreting the data regarding "relatedness". As discussed above,, use of PUT data is not optimal in determining sensitization, as maximal provocation is generally used to bring out the real potential of the product.*

• Significant Protocol Changes relating to Dermal Safety Evaluation. There are several changes to be noted:

- The terminology used for the scoring system for irritation/sensitization reactions was clarified. (Nov 6, 1996)
- Sensitization testing schedule amended to "more closely reflect standard procedures. Due to blinding issues, all patients were to be tested for sensitization." (Nov 6, 1996)

- During the time interval (2-4 weeks) between the Treatment Phase and the Sensitization Testing Phase, patients were told to only take acetaminophen for pain relief in order to avoid the use of NSAIDs. (Feb 17, 1997)
- Patients with psoriasis, but ***not*** at the site of application, could be included (Criterion #5 had prevented enrollment) (Feb 17, 1997)
- If a patient developed skin irritation that was evaluated at a score of 3 or 4, the investigator was asked to discontinue treatment, and to ensure that patients did not continue to apply the lotion to skin that was irritated to this level. (Feb 17, 1997)

Results:

The study was conducted 1/7/97 to July, 1997.

Comment *A specific date of completion of this study cannot be found in the material provided. It is noted that substantive protocol amendments were developed as late as in May, 1997. According to Section 9.8 of the report (vol 8.14, pages 56 to 60), there was also an amendment on November 6, 1997, which could be a typographic error. It is difficult to conceive of the impact of the late protocol changes on the conduct of the study; it appears that the Investigators would be following different procedures at different times of the study.*

- Investigators:

b(4)

Comments
1. Although this is a multi-center trial, it actually covers a relatively small geographic region in Southern Ontario, Canada. The applicability of the clinical study data to the diverse population in the United States should be addressed by the Applicant.
2. The qualifications of the Investigators have not been included in this consult and therefore not reviewed.

- Subject Disposition and Demographics: Randomized 267 patients, and 248 received one of the three

treatments (PENNSAID 84, Control 80, and Placebo 84), with 209 completing the Treatment Phase (PENNSAID 74, Control 66, and Placebo 69). The withdrawals are shown as follows:

	PENNSAID	Control	Placebo
Total Withdrawal	10	14	15
Reasons*:			
• Lack of efficacy	2	9	9
• Poor tolerance to test drug	5	5	1
• Failure to appear for scheduled appt	0	2	2
• Insufficient/unreliable patient cooperation	0	3	1
• Protocol violation	1	0	4
• Other – medical reason	1	0	4
	0	1	1

• Other – non-medical reason			

*Withdrawal could be due to more than one reason in a patient.

Comment *This Table shows "Poor Tolerance to Study Medication" leading to discontinuation in 11 patients (PENNSAID 5, Control 5 and Placebo1). However, the safety conclusion section (Section 13; vol 8.14, page 215) states that only 2 patients given PENNSAID, 3 given control and none given placebo dropped out for this reason. The discrepancy is unexplained.*

For Sensitization Testing Phase, 145 patients participated (PENNSAID 53, Control 47, and Placebo 45), and 139 completed (PENNSAID 49, Control 46, and Placebo 44). The 6 withdrawals in this phase were either due to "insufficient and/or unreliable patient" (PENNSAID 1 and Control1), or "protocol violation (Investigator error)" (PENNSAID 3 and Placebo 1).

The demographic data of the enrolled patients showed:

	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
Age (Mean ± SD)	62.5 ± 11.7	62.1 ± 11.4	60.8 ± 11.4
Males	32	26	33
Females	52	54	51
White	79	74	76
Black	1	3	3
Asian	4	3	5

- Irritancy Scoring during Treatment Phase:

Scores in Irritation Assessment in Treatment Phase

Worst Irritation Scores	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
0	72	75	83
0.5	3	1	1
1	7	4	0
2	1	0	0
3	1	0	0
4	0	0	0

- Results of Sensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
Challenge	16/49	9/46	0/44
Rechallenge	12/16	7/9	0/0
PUT	0/12	1/7	0/0

- Adverse Event Reporting: Few adverse events were considered "related". The following have been reported:

"Related" Adverse Events Not Classified under Skin & Appendages in Study 107-96 (From Table #82 pp 153-4)

	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
Body odor	2 (2.38%)	0	0
Halitosis	4 (4.76%)	1 (1.25%)	0
Vasodilation at application site	0	1 (1.25%)	0
Taste perversion	4 (4.76%)	3 (3.75%)	4 (4.76%)
Paresthesia at application site	12 (14.29%)	18 (22.50%)	5 (5.95%)

Adverse Events Classified under Skin & Appendages in Study 107-96 (From Table #82 pp 153-4)

	PENNSAID (N=84)		Control (N=80)		Placebo (N=84)	
	"Related"	"Not Related"	"Related"	"Not Related"	"Related"	"Not Related"
Dry skin	0	0	0	0	0	1 (1%)
Dry skin at application site	30 (36%)	0	11 (14%)	0	1 (1%)	0
Herpes simplex	0	0	0	0	0	1 (1%)
Pruritus	0	2 (2%)	0	5 (6%)	0	1 (1%)
Pruritus at application site	9 (11%)	0	6 (8%)	0	3 (4%)	0
Rash	0	3 (4%)	0	2 (3%)	0	2 (2%)
Rash at application site	11 (13%)	0	6 (8%)	0	3 (4%)	0
Sweating	0	0	0	1 (1%)	0	0
Urticaria	0	1 (1%)	0	1 (1%)	0	0
Vesiculobullous rash	1 (1%)	0	0	0	0	0

There were 52.4% (44/84) patients in the PENNSAID arm who had "related" adverse events reported. However, only 24 of these patients (28.6%) had documentation in the diary.

Comment

1. The Applicant argues that the reporting rate for "related" adverse events of 52.4% is exaggerated, as it includes a large number of cases with minor dry skin at the application site thought to be not significant by the patient, and thus not recorded in diary. The diary entry sheet has this reminder for each day: "Please record any abnormal event you think may be related to the use of the study medication that happened during the last 24 hours." The Applicant asserts that -

> *"... an adverse event is something experienced by the patient and most accurately reported by that patient, not by an outside observer and that the diary reports, with a frequency of 28.6%, be accepted as the most reasonable and correct estimate of skin-related adverse events."*

As discussed above, the definition of "relatedness" by the Applicant is questionable. Here the Applicant advocates that patient reporting should be considered most accurate and a lower rate of "related" adverse events be accepted on the basis of diary entries. While it is reasonable that an adverse event should be a finding that has occurred in the patient, not all adverse events are experienced (e.g., cancer, internal congenital anomaly, laboratory abnormality). In this study, the study coordinator asked about specific adverse events from a checklist, and this is a more sensitive technique than the patient diary in soliciting events "experienced" by the patient. An examination of the reported items shows that all

of them which were reported by the 44 patients (52.4%) could have been subjectively experienced, not just observed by the study coordinator.
2. Many cases of "dry skin" actually involved reporting of peeling, scaling and flakiness (Table #310; vol 8.14, pages 421-432). Use of the term "dry skin" may be confusing.

Deaths, Serious Adverse Events and Other Significant Adverse Events. No deaths were reported in this study. Serious adverse events and other significant adverse events are listed in Tables #311 and #312 (vol 8.14, pages 434-440). There were two serious adverse events: aphasia/confusion secondary to cerebrovascular accident (#1032; 74 year old female) and arrhythmia (#4023; 66 year-old male). Both were on PENNSAID, and in the former case, treatment was discontinued. Other significant adverse events can be summarized in the following Table:

Patient ID	Age	Sex	Adverse Event	Test Drug /Discontinuation?
1039	76	F	Pruritus/headache	Control/yes
1040	72	F	Rash/pruritus	PENNSAID/yes
1046	37	F	Pain/back pain	Placebo/yes
1054	71	F	Arthralgia	PENNSAID/yes
1065	71	M	Arthralgia/paresthesia	Control/yes
1069	74	M	Asthenia/palpitation	PENNSAID/yes
1077	46	F	Rash/pruritus/vesiculobullous rash	PENNSAID/yes
3012	68	M	Arthralgia/ headache	Placebo/yes
4011	72	F	Backpain/arthralgia	Placebo/yes
4010	50	F	Pharyngitis/ear infection	Placebo/yes
4031	59	F	Rash/arthrosis/face edema/dyspepsia/headache/malaise	PENNSAID/yes
5008	54	F	Arthrosis	Placebo/yes
5010	65	F	Paresthesia/dry skin	Control/yes
5012	60	M	arthrosis	Placebo/yes
6006	48	M	Pruritus/arthralgia	PENNSAID/yes
6014	58	M	Body odor/halitosis	PENNSAID/yes
6018	69	F	Peipheral edema	Control/yes
6024	69	F	Arthrosis/headache/taste perversion	Control/yes

- Clinical Laboratory Testing. The only clinical laboratory test that showed significant differences in abnormal

findings between treatment arms was alanine aminotransferase (ALT/SGPT). A greater number of patients treated with control lotion (4) had changes from normal to abnormal than in other groups (1 with PENNSAID and 0 with Placebo):

Changes in ALT Levels from Normal to Outside Normal Range in Study 107-96

	PENNSAID	Control			
Patient ID	4040	1048	3011	3034	4025
Pre level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	<55	<55	<42	<42	<55

b(4)

Comments *The changes in Patients #4040 and #1048 were 3 fold or higher above baseline, although they were within 3x upper limit of normal range. The changes in these*

two patients were also accompanied by substantial changes in AST/SGOT (from ——— in #4040, and from ——— in #1048; normal <45 in both laboratories). Although diclofenac use may be associated with liver enzyme changes, DMSO is believed to be protective against liver toxicity induced by some hepatotoxins. Without details on the systemic availability of these components upon topical use, it is difficult to interpret the data from these two cases. Transaminase elevation due to topical use of diclofenac has neither been ruled in or ruled out.

b(4)

Conclusions:

The study report states:

> "Other than minor local skin irritation, no significant safety issues were identified in this study. ..... data suggest a minor, local irritation by the 45% DMSO which is common to only the PENNSAID™ and control study lotions; this observation is neither new, surprising or of great clinical significance. If 2.4% (2/84) of patients, for whom PENNSAID™ will be prescribed, discontinue to the lotion, this would not be an excessive or unusual rate for any drug." (vol 8.14. page 215)

Comments

1. This study was not properly designed to determine sensitization potential. PUT is not an adequate methodology for this purpose, and patients did not undergo appropriate induction. Despite this, 12/49 (24.5%) patients treated with PENNSAID and 7/46 (15.2%) with its vehicle containing DMSO had positive reaction upon rechallenge. Although DMSO in the vehicle is an irritant, the additional reactions observed with PENNSAID rechallenge are consistent with data from the phase 1 studies. As a preparation containing diclofenac but not DMSO has not been tested, it is not possible to distinguish between irritation and sensitization from this testing.

2. It appears to be inaccurate to state that only 2/84 patients given PENNSAID discontinued due to the treatment. Although the Applicant dismisses 2 cases of pruritus and 3 cases of rash as being "not related", at least 5 patients who discontinued PENNSAID had adverse events that could be due to the treatment:

#1040 Rash/pruritus
#1077 Rash/pruritus/vesiculobullous rash
#4031 Rash/arthrosis/face edema/dyspepsia/headache/malaise
#6006 Pruritus/arthralgia
#6014 Body odor/halitosis

3. Desquamation, variably described as peeling, scaling, and flaking, but coded as "dry skin" in this report, is a prominent adverse event (36% PENNSAID patients and 14% control patients). However, this event was minimized by the Applicant as being "minor". Paresthesia, rash, and pruritus at the application site, as well as halitosis and body odor were the other "related" adverse events in patients treated with PENNSAID.

4. Systemic availability and internal organ toxicity cannot be determined by this study. Although the cause of transaminase elevation in a patient treated with PENNSAID in this study cannot be determined, it is known that diclofenac used orally may be associated with liver toxicity. Enzyme elevation has been observed in 4% of 3700 patients treated in a large trial for 2 to 6 months (Voltaren label).

Summary and Conclusions

This NDA presents an NSAID, diclofenac, in a solution containing DMSO (PENNSAID Solution) for the treatment of osteoarthritis.

Five studies have been reviewed in this consult: four phase 1 dermal safety studies and one phase 3 trial on the safety and efficacy of PENNSAID Lotion in the treatment of osteoarthritis, with sensitization testing in a subset of patients after the treatment period. The phase 1 studies examined the potential of PENNSAID Lotion for irritancy, contact sensitization, photoirritation, and photoallergenicity. In each of the five studies, in addition to the PENNSAID Lotion, two other test products were applied: Placebo-H (Placebo-1), which was the vehicle lotion without diclofenac, and Placebo-L (Placebo2), a vehicle containing a low strength of DMSO (1/10 of the concentration in PENNSAID or in Placebo-H). The studies were:

Phase 1
100-89. Primary cumulative skin irritation potential of PENNSAID® Topical Lotion
101-89-2. Skin sensitization study of PENNSAID® Topical Lotion
103-93-2. A skin photoirritation potential of PENNSAID® Topical Lotion
104-93-3. A modified Draize photosensitization study of PENNSAID® Topical Lotion
Phase 3
107-96. A double-blinded, placebo-controlled, three-way parallel clinical trial to confirm the safety and efficacy of PENNSAID® treatment and to compare two methods of measuring pain of the osteoarthritic knee

The results of the studies can be summarized in the following Tables. Data from Study 103-93-2 are not shown, as there were no positive reactions in photoirritation testing.

Mean Irritancy Scores in the Induction Phase

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89 (N=23)	0.300 ± 0.764	0.158 ± 0.378	0.051 ± 0.172
	P-values (one-way ANOVA): PENNSAID vs Placebo-1=0.272, PENNSAID vs Placebo-2=0.057, Placebo-1 vs Placebo-2=0.406.		
101-89-2 (N=206)	0.030 ± 0.226	0.009 ± 0.091	0.005 ± 0.077
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.105, PENNSAID vs Placebo-L=0.062, Placebo-H vs Placebo-L=0.805.		
104-93-2 (N=27)	0.042 ± 0.109	0.040 ± 0.123	0.017 ± 0.069
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.873, PENNSAID vs Placebo-L=0.113, Placebo-H vs Placebo-L=0.153.		
107-96	Safety and efficacy study with no induction phase		

Positive Challenge and Rechallenge Rates

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89			
Challenge Rechallenge (% positive)*	4/23 3/6 (13.0%)	6/23 1/4 (4.3%)	2/23 0/3 (0)
101-89-2			
Challenge Rechallenge (% positive)	8/204 5/8 (2.5%)	5/206 3/5 (1.5%)	1/205 0/1 (0)
104-93-3			

Challenge (non-irradiated vs irradiated) Rechallenge (non-irradiated vs irradiated) (% positive)	8/27 vs 7/27 5/8 vs 5/8 (18.5%)	6/27 vs 5/27 3/6 vs 3/5 (11.1%)	2/27 vs 2/27 1/3 vs 1/3 (3.7%)
107-96			
Challenge Rechallenge (% positive)	16/49 12/16 (24.5%)	9/46 7/9 (15.2%)	0/44 0/0 (0)

*% positive is calculated by dividing the number of subjects with positive rechallenge reactions by the total who underwent challenge.

The following Conclusions can be drawn from the material reviewed:

1. The dermal safety studies should be done on the to-be-marketed formulation. As the product proposed for marketing is a "solution", and the studies reviewed used a "lotion", it is unclear whether they represent the same product, even if the compositions are the same. The solubility of the ingredients may affect safety and efficacy, and hence the applicability of the conclusions to be drawn from the studies to the marketing formulation.

2. The dermal safety studies were not conducted under GLP, and the study reports contain internal inconsistencies. The design of the studies appears to be acceptable to obtain the needed information on the potential for dermal toxicity, although the provocation use test (PUT) in these studies is both inadequate and unnecessary. The Applicant has not presented their rationale in conducting photoirritation and photosensitization studies, which could be waived if none of the components of the drug product absorb in the UV-B, UV-A or the visible spectrum. However, it is known that diclofenac does absorb in the UV-B spectrum.

3. Dermal safety studies are usually performed on normal skin at the back or upper extremities in healthy volunteers. Caution should be exercised in the extrapolation of their data to other anatomic regions in specific patient groups. For instance, there was a much higher positive reaction rate in the sensitization testing in the phase 3 trial, 107-96, than in the contact sensitization study, 101-89-2. It is unclear whether differences in the population (older patients and overwhelming Caucasians in 107-96), previous therapies or the disease itself could be factors contributing to these variations.

4. It should be emphasized that contact sensitization testing involves a type IV dermal reaction for delayed hypersensitivity. Immune mechanisms such as anaphylaxis or other antibody-mediated reactions would not be tested by the studies submitted.

5. The data from the four dermal safety studies in this application suggest that PENNSAID Lotion is of low photoirritation and photosensitization potential. However, DMSO is by itself a known irritant, and the data suggest that the presence of diclofenac enhanced irritancy of the product. Interpretation of the sensitization testing data is complicated by the irritancy effect of DMSO and diclofenac (positive rates of 2.5%-18.5% for PENNSAID and 1.5%-11.1% for vehicle). In the phase 3 study, 107-96, the rates were even higher (24.5% for PENNSAID and 15.2% for vehicle). As a preparation containing diclofenac but not DMSO has not been tested, it is not possible to distinguish

between irritation and sensitization from these studies. Because of this, the sensitization potential of PENNSAID is not excluded, but not proven.

6. One serious adverse event was reported in the four dermal safety studies (death due to cancer in 101-89-2). Other than skin test reactions, no other adverse events have been noted. Adverse event reporting in these studies appears to be inadequate. In the phase 3 trial, Study 107-96, the adverse events leading to discontinuation that might be related to the use of PENNSAID were rash, pruritus, halitosis and body odor, while desquamation ("dry skin") was observed in more than a third of patients. These risks should be carefully weighed against the benefits.

7. Systemic safety depends on systemic bioavailability, and would be supported by PK data, adverse event reporting, and clinical laboratory testing. The reviewed material does not contain PK information. In the phase 3 trial, Study 107-96, adverse event reporting and lab tests suggest that PENNSAID Lotion was well tolerated in general. Although transaminase elevation was observed in a patient using PENNSAID Lotion, its relationship to treatment is uncertain. Systemic exposure data would be helpful to determine whether the toxicities of oral diclofenac preparations, including liver toxicity, should be seriously considered for PENNSAID Lotion or not.

APPENDIX #2

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

DATE: **July 15, 2002**

FROM: Claudia B. Karwoski, Pharm.D.,
Safety Evaluator Team Leader
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

SUBJECT: Postmarketing Safety Review—PID
Drug: Topical Diclofenac (Pennsaid®, NDA 20947)
Reaction: Review of AERS cases

INTRODUCTION/EXECUTIVE SUMMARY

In response to a request by Dr. Tatiana Oussova, MD of the DAAODP, we reviewed adverse event cases in AERS reported in association with topical diclofenac. Specially, they were interested in any signals indicating a likely association of topical diclofenac with serious adverse reactions such as gastrointestinal (GI) bleed, serious skin reactions, and hematological, renal or cardiac events. DAAODP is currently reviewing an application for this product. The product has been available in Europe but the sponsor did not submit postmarketing data from overseas.

We reviewed 31 cases of adverse events reported in association with the use of topical diclofenac. Many of the reactions were serious in nature including seven deaths. The types of events included local reactions as well as systemic reactions including serious skin reactions, hematological, GI events, and several miscellaneous adverse events. In general, these cases were poorly documented or were confounded by the condition that they were treating, other medication, concurrent non-medication therapies, or possibly by underlying disease.

SELECTION OF CASES

We searched AERS on June 27, 2002 for diclofenac reports with the following routes of administration – *cutaneous, occlusive dressing technique, topical, transdermal,* and *other.* One hundred thirty-two cases were retrieved, of which 6 were duplicates for a total of 126 cases. We excluded 95 for the following reasons:

- Reports involving other diclofenac formulations - 95
  - Cases involving diclofenac ophthalmic preparations - 71
  - Reports involving oral diclofenac with concomitant topical products – 14
  - Reports involving diclofenac tablets/ampoules/suppositories/unknown formulations – 10

SUMMARY OF CASES

We reviewed 31 cases of adverse events reported in association with topical diclofenac. In general the cases were not well documented and because they were all foreign, pertinent information might have been lost during translation. The countries of origin included France-16, Germany-10, Hong Kong-1, Japan-1, Israel-1, Spain-1, and the United Kingdom-1.

Local reactions (12)

The local reactions included the following:
Skin necrosis (5)
Burns (2)
Application site reaction (2)
Infection of the forefinger (1)
Bleeding wound, localized inflammation (1)
Sensory disturbance (1)

There were five cases of skin necrosis that appeared to occur at the site of diclofenac application. Three patients were hospitalized, two of which required skin grafting. Two specified that the scarring occurred as a result of the necrosis and one patient reportedly lost the use of her legs. In 2 of the 5 cases, there were additional factors that might have contributed. In one case the patient was undergoing phonophoretic treatment using Voltaren Emulgel as the contact gel. The company for the instrument actually reported the case. The second reported the concurrent treatment of oral Fucidine (fusidic acid) and diclofenac gel for a swollen and warm wound following varicose vein stripping. Eight days after treatment with both products, the patient developed fever and skin necrosis of 15cm diameter. The case that appeared to be the most serious is summarized below.

AERS 3607694-9, MFR # PHRM2000FR01562, France, 2000
An 88-year-old female developed necrotic purpura of both legs sometime during Voltaren Emulgel treatment for gonarthrosis. She was hospitalized for three months, during which time she underwent grafting of the necrotic areas. She reportedly lost the use of her legs and was hospitalized long term.

There were two cases involving skin burns and two cases that reported application site reactions. The burns were described as second or third degree burns. The two application site reactions were described as erythema, burning sensation, and edema in one case and

redness, swelling, and pain in the second case. In 3 of the 4 cases, concurrent physical electrotherapy, iontophoresis, or kinesitherapy appeared to play a role. In both burn cases, allergy testing showed no sensitivity to Voltaren Emulgel.

There was one case involving an elderly female that was treated with both topical diclofenac and oral piroxicam for six days for a finger nodule and developed a local infection and leg edema. Both medications were discontinued and she was treated with antibiotics, tetanus vaccine, and diuretics but reportedly required phalanx amputation.

An elderly female patient reported a bleeding wound and localized inflammation of her right calf. She had reportedly taken topical diclofenac without a prescription for calf pain. The diclofenac did not relief the calf pain and subsequently she developed an open wound. She was hospitalized and diagnosed with occlusive artery disease.

A 61-year-old male with myalgia developed considerable sensory disturbances and hematoma in the lumbar region of the back and at the right hip after application of Voltaren Emulgel. The patient was receiving several concomitant medications including aspirin. Hospitalization was not required but symptoms at the time of the report were still persisting.

Serious Skin Reactions (7)

The systemic skin reactions included Stevens Johnson syndrome (SJS) or Lyell Syndrome (3), necrotizing fasciitis (1), pemphigus (1), toxic allergic reaction (1), and maculopapular rash (1). Three patients died and three were hospitalized for their events. In two of the cases of SJS, the role of topical diclofenac was impossible to assess because multiple suspect drug products were listed (10 and 33 suspect drugs).

A case of Lyell syndrome and necrotizing fasciitis both resulting in death are described below.

FDA 980880, MFR # 930201-001, France, 1992
A 77 year-old male developed Lyell syndrome. This was apparently discovered as part of an E.L.Y.S survey, the details of which were not provided. According to the report, he was applying Voltaren Emulgel twice per day for an unknown period of time for arthrosis pain. The exact dates of administration in relation to the onset of the event were not provided. One month before hospitalization, he developed pruritus of the face, which was treated with corticoldes [sic] (presumably corticosteroids) and anithistamines. He was admitted with erythematous lesion on his face, thorax, and back. He also had buccal erosions but no genital or ocular lesions. He apparently died five days after admission.

FDA 1594520, MFR # 951030-001, Germany, 1994
An 81-year-old female experienced a fall and four days later presented with right arm pain. She was prescribed Voltaren Emulgel. One day later, she presented again with severe continuous pain in the right arm. The arm was swollen and she was hospitalized. A few hours later skin necrosis developed and she underwent fasciotomy. She developed

circulatory instability and developed massive metabolic acidosis. The necrosis spread all over her body and she died a few days later from septic shock.

Although it was possible that topical diclofenac played a role in these two cases, the first case was not well documented with respect to the dates of administration and the event date. For the second case, it seems feasible that this event could have occurred as a result of the trauma itself. This case did not mention whether the patient developed compartment syndrome or an equally serious injury and it is not clear whether use of topical diclofenac might have exacerbated this event.

In 2 of the 3 remaining cases, hospitalization was required and the patients were improving on discontinuation of topical diclofenac and other suspected medications. The first involves an elderly woman who developed dysphagia and painful oral and pharyngeal ulcers of three months duration. She had been taking both topical diclofenac and diclofenac suppositories for a number of years. An oral mucosal biopsy was positive for pemphigus vulgaris. A migration inhibition factor test performed with the patient's lymphocytes yielded a positive response to diclofenac. A second case involved a man who developed a toxic allergic reaction after two days of topical diclofenac. No concomitant medications were reported. The reaction was described by the patient as "red skin with fever and chills" and by the physician as "resembling a second-degree burn". There was a case of maculo-papular and vesicular rash reported in association with topical diclofenac and hydergine. The patient was also on other concomitant medications. All medications were discontinued and patient recovered.

Gastrointestinal Reactions (2)

The GI reactions included gastric perforation (1) and GI bleed (1). One patient died and the other required hospitalization. In both cases, the GI events may have been caused by concomitant use of oral NSAIDS. The death case is described below.

FDA 821654, MFR # S8814061, Germany, 1988
A 78-year-old male was hospitalized and died following gastric perforation. He was receiving Voltaren Emulgel for lumbosacral spondylosis. He was also on concomitant oral and parenteral Effekton Retard (diclofenac), which was felt by the reporter to be more likely responsible for the event.

In addition to the case of gastric perforation described above, there is one case of GI bleeding (reported melena, hematemesis, and a decrease in hematocrit) in a 69-year-old male who was receiving topical diclofenac for approximately one week for arthralgias. The patient was also receiving aspirin 500mg per day for an unknown period of time for headache.

Drug Interaction (2)

There were two cases that reported a possible drug interaction between an anticoagulant (acenocoumarol and warfarin) and topical diclofenac. In one case an 86-year-old female

who had been on acenocoumarol for years for a cardiac valve disorder, was placed on topical diclofenac for two days. She developed a left shoulder hematoma that extended to her left arm and breast. Her INR was elevated to 4.5. Topical diclofenac was discontinued, her anticoagulant dose was decreased, and her INR subsequently returned to normal. In the second case a 68-year-old male receiving warfarin for a heart valve replacement was placed on diclofenac gel for joint pain. On day 5 of diclofenac treatment, his INR was 4.0. No further information was provided.

Hematological Reactions (2)

The hematological reactions included hemolytic anemia/thrombocytopenia (1) and agranulocytopenia/thrombopenia (1). One patient died and the other required hospitalization. The death case is described below

FDA 1361653, MFR # 930676-001, Great Britain, 1993
A 75-year-old female with chronic myelomonocytic leukemia was treated with transdermal Voltarol for 89 days and developed autoimmune hemolytic anemia and thrombocytopenia. Laboratory data however was not provided. Her concomitant medication included Co-proxamol (dextropropoxyphene/acetaminophen), isosorbide mononitrate, and aspirin. She was treated with prednisolone 40mg per day and the reaction abated with discontinuation of diclofenac. She later died due to a pulmonary embolus. The time that elapsed between the onset of the event and her death was not evident.

In the second case, four suspect drugs were listed with the most likely agent being colchicine.

Miscellaneous Reactions (6)

The miscellaneous reactions included hypersensitivity/disseminated intravascular coagulation (1), status epilepticus/cardiac arrest (1), renal failure (1), rhabdomyolysis (1), spontaneous abortion (1), and hyponatremia (1). Two patients died and the other four required hospitalization. In the first four cases listed above, the role of topical diclofenac was impossible to assess because multiple suspect drug products were listed (6 to 18 suspect drugs).

There was one case of a 40-year-old female who had a spontaneous abortion at 12 weeks gestation. She was treated sometime during her pregnancy with topical diclofenac for an unknown reason but the treatment dates and duration were unknown. She was taking no other medication and had one previous child who died from chondrodysplasia fetalis.

There was one case of hyponatremia (Na 113 mmol/L) reported in a 71-year-old female with a history hypothyroidism. There was a question of compliance with her thyroid replacement therapy. Fluoxetine, which is labeled for hyponatremia, was also suspected and was temporally related to the event. She was hospitalized and all medications except levothyroxine were discontinued.

CONCLUSION

We reviewed 31 cases of adverse events reported in association with the use of topical diclofenac. Many of the reactions were serious in nature including seven deaths. The types of events included local reactions as well as systemic reactions including serious skin reactions, hematological, GI events, and several miscellaneous adverse events. In general, these cases were poorly documented or were confounded by the condition that they were treating, other medication, concurrent non-medication therapies, or possibly by underlying disease.

Claudia B. Karwoski, Pharm.D

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

/s/

Tatiana Oussova
8/6/02 12:17:55 PM
MEDICAL OFFICER

Lee Simon
8/7/02 09:34:10 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

Tel 301-827-2020
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MEMORANDUM

Date: May 16, 2002

From: Hon-Sum Ko, M.D., Medical Officer HSK 5-16-02

Through: Susan Walker, M.D., Dermatology Team Leader and SW 5-20-02
Jonathan K. Wilkin, M.D., Division Director JW 5/22/02

To: Lee Simon, M.D., Division Director, HFD-550

Re: Consult 293 (DDDDP#029788) dated 2/8/02 and resent 2/26/02 from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products and assigned 2/15/02. In the Request for Consultation, the box "Safety/Efficacy" under "I. General" has been checked off. The COMMENTS/SPECAIL INSTRUCTIONS box gives:

"Please forward all comments and review to Nancy Halonen, Project Manager, HFD-550 Rm N313, ext. 7-2019

"Since this is the first NSAID topical analgesia/anti-inflammatory that may be approved from HFD-550, we need to be sure that this has a complete and proper review of all aspects of safety and efficacy. We would like the derm consult to help in this effort and hope that part of that will include an assessment and opinion as to whether the types of studies submitted by the sponsor are sufficient towards an NDA approval. In other words, not only are the submitted studies adequate to demonstrate safety but are these studies complete in addressing all the usual aspects of safety that should be considered in this regard."

This consult is on NDA 20-947, PENNSAID (diclofenac sodium 1.5%) Solution from Dimethaid Research, Inc. of Markham, Ontario, Canada, originally submitted 12/15/97, withdrawn 10/26/98, and resubmitted 8/7/01. Due to a major amendment received on 3/29/02, PDUFA goal dates are: 9/8/02 (primary), & 11/8/02 (secondary).

Material Reviewed

NDA 20-947 Volumes 8.11 through 8.14, and the following Electronic files:

- Item 2: Labeling, and
- Item 8: Clinical Data: Sections A.4a (List of INDs), D-E (Table of All Controlled Clinical Studies), and H (Integrated Summary of Safety)

Executive Summary

This NDA presents an NSAID, diclofenac, in a solution containing DMSO (PENNSAID Solution) for the treatment of osteoarthritis.

Five studies have been reviewed in this consult: four phase 1 dermal safety studies and one phase 3 trial on the safety and efficacy of PENNSAID Lotion in the treatment of osteoarthritis, with sensitization testing in a subset of patients after the treatment period. The phase 1 studies examined the potential of PENNSAID Lotion for irritancy, contact sensitization, photoirritation, and photoallergenicity. In each of the five studies, in addition to the PENNSAID Lotion, two other test products were applied: Placebo-H (Placebo-1), which was the vehicle lotion without diclofenac, and Placebo-L (Placebo2), a vehicle containing a low strength of DMSO (1/10 as in PENNSAID or in Placebo-H). The studies were:

Phase 1
100-89. Primary cumulative skin irritation potential of PENNSAID® Topical Lotion
101-89-2. Skin sensitization study of PENNSAID® Topical Lotion
103-93-2. A skin photoirritation potential of PENNSAID® Topical Lotion
104-93-3. A modified Draize photosensitization study of PENNSAID® Topical Lotion
Phase 3
107-96. A double-blinded, placebo-controlled, three-way parallel clinical trial to confirm the safety and efficacy of PENNSAID® treatment and to compare two methods of measuring pain of the osteoarthritic knee

The results of the studies can be summarized in the following Tables. Data from Study 103-93-2 are not shown, as there were no positive reactions in photoirritation testing.

Mean Irritancy Scores in the Induction Phase

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89 (N=23)	0.300 ± 0.764	0.158 ± 0.378	0.051 ± 0.172
	P-values (one-way ANOVA): PENNSAID vs Placebo-1=0.272, PENNSAID vs Placebo-2=0.057, Placebo-1 vs Placebo-2=0.406.		
101-89-2 (N=206)	0.030 ± 0.226	0.009 ± 0.091	0.005 ± 0.077
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.105, PENNSAID vs Placebo-L=0.062, Placebo-H vs Placebo-L=0.805.		
103-93-2 (N=27)	0.042 ± 0.109	0.040 ± 0.123	0.017 ± 0.069
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.873, PENNSAID vs Placebo-L=0.113, Placebo-H vs Placebo-L=0.153.		
107-96	Safety and efficacy study with no induction phase		

Positive Challenge and Rechallenge Rates

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89			
Challenge Rechallenge (% positive)*	4/23 3/6 (13.0%)	6/23 1/4 (4.3%)	2/23 0/3 (0)
101-89-2			
Challenge Rechallenge (% positive)	8/204 5/8 (2.5%)	5/206 3/5 (1.5%)	1/205 0/1 (0)
104-93-3			
Challenge (non-irradiated vs irradiated) Rechallenge (non-irradiated vs irradiated) (% positive)	8/27 vs 7/27 5/8 vs 5/8 (18.5%)	6/27 vs 5/27 3/6 vs 3/5 (11.1%)	2/27 vs 2/27 1/3 vs 1/3 (3.7%)
107-96			
Challenge Rechallenge (% positive)	16/49 12/16 (24.5%)	9/46 7/9 (15.2%)	0/44 0/0 (0)

*% positive is calculated by dividing the number of subjects with positive rechallenge reactions by the total who underwent challenge.

The following Conclusions can be drawn from the material reviewed:

1. The dermal safety studies should be done on the to-be-marketed formulation. As the product proposed for marketing is a "solution", and the studies reviewed used a "lotion", it is unclear whether they represent the same product, even if the compositions are the same. The solubility of the ingredients may affect safety and efficacy, and hence the applicability of the conclusions to be drawn from the studies to the marketing formulation.

2. The dermal safety studies were not conducted under GLP, and the study reports contain internal inconsistencies. The design of the studies appears to be acceptable to obtain the needed information on the potential for dermal toxicity, although the provocation use test (PUT) in these studies is both inadequate and unnecessary. The Applicant has not presented their rationale in conducting photoirritation and photosensitization studies, which could be waived if none of the components of the drug product absorb in the UV-B, UV-A or the visible spectrum. However, it is known that diclofenac does absorb in the UV-B spectrum.

3. Dermal safety studies are usually performed on normal skin at the back or upper extremities in healthy volunteers. Caution should be exercised in the extrapolation of their data to other anatomic regions in specific patient groups. For instance, there was a much higher positive reaction rate in the sensitization testing in the phase 3 trial, 107-96, than in the contact sensitization study, 101-89-2. It is unclear whether differences in the population (older patients and overwhelming Caucasians in 107-96), previous therapies or the disease itself could be factors contributing to these variations.

4. It should be emphasized that contact sensitization testing involves a type IV dermal reaction for delayed hypersensitivity. Immune mechanisms such as anaphylaxis or other antibody-mediated reactions would not be tested by the studies submitted.

5. The data from the four dermal safety studies in this application suggest that PENNSAID Lotion is of low photoirritation and photosensitization potential. However, DMSO is by itself a known irritant, and the data suggest that the presence of diclofenac enhanced irritancy of the product. Interpretation of the sensitization testing data is complicated by the irritancy effect of DMSO and diclofenac (positive rates of 2.5%-18.5% for PENNSAID and 1.5%-11.1% for vehicle). In the phase 3 study, 107-96, the rates were even higher (24.5% for PENNSAID and 15.2% for vehicle). As a preparation containing diclofenac but not DMSO has not been tested, it is not possible to distinguish between irritation and sensitization from these studies. Because of this, the sensitization potential of PENNSAID is not excluded, but not proven.

6. One serious adverse event was reported in the four dermal safety studies (death due to cancer in 101-89-2). Other than skin test reactions, no other adverse events have been noted. Adverse event reporting in these studies appears to be inadequate. In the phase 3 trial, Study 107-96, the adverse events leading to discontinuation that might be related to the use of PENNSAID were rash, pruritus, halitosis and body odor, while desquamation ("dry skin") was observed in more than a third of patients. These risks should be carefully weighed against the benefits.

7. Systemic safety depends on systemic bioavailability, and would be supported by PK data, adverse event reporting, and clinical laboratory testing. The reviewed material does not contain PK information. In the phase 3 trial, Study 107-96, adverse event reporting and lab tests suggest that PENNSAID Lotion was well tolerated in general. Although transaminase elevation was observed in a patient using PENNSAID Lotion, its relationship to treatment is uncertain. Systemic exposure data would be helpful to determine whether the toxicities of oral diclofenac preparations, including liver toxicity, should be seriously considered for PENNSAID Lotion or not.

Introduction

This consult request s (a) an **assessment** and **opinion** as to whether the types of studies are sufficient, and (b) whether the studies are **complete** in addressing all the usual aspects of safety that should be considered towards NDA approval.

PENNSAID® (diclofenac sodium) Topical Solution, 1.5%, in NDA 20-947 has the proposed indication of ——— The unit formula and representative ——— batch formula are: b(4)

Composition of PENNSAID® Topical Solution (1.5% w/w diclofenac sodium, [DMI-F0001 ———			
Ingredients	**mg/g**	**kg/batch**	**%**
Diclofenac sodium USP	15.0		1.5
Dimethyl Sulfoxide USP	455.0		45.5
Glycerin —— USP			
Propylene Glycol USP			
Alcohol, —— USP			
Purified Water USP			
Total Weight of PENNSAID® Topical Solution			100.0

b(4)

Comments

1. The volumes requested for review (8.11-8.14) contain reports on four phase 1 dermal safety studies (100-89, 101-89-2, 103-93-2, 104-93-3) and one phase 3 safety/efficacy study (107-96), which includes testing sensitization in a subset of patients. A ***complete*** *evaluation of* ***all aspects of safety to support an NDA approval*** *is neither possible nor appropriate for this consult. Only the Medical Officer of this NDA has access to all the clinical data and the familiarity with the proposed indication to determine all aspects of safety in conjunction with the product's efficacy for a proper risk-benefit analysis. This consult report will be confined to addressing the dermal safety testing.*

2. The drug product contains 45.5% dimethyl sulfoxide, believed to enhance absorption of diclofenac through the skin. An evaluation of the reported adverse effects of dimethyl sulfoxide solution has been requested of ODS.

3. The drug product is said to be a "solution" in this application. However, in the five clinical studies requested for review, the product tested is said to be a "lotion". As the terminology for the dosage form differs between what has been studied and what is intended for marketing, it is unclear whether the formulations studied and the to-be-marketed product are identical in all aspects, even if the compositions are the same.

The Studies presented for review in this consult are:

Phase 1

100-89. Primary cumulative skin irritation potential of PENNSAID® Topical Lotion

101-89-2. Skin sensitization study of PENNSAID® Topical Lotion

103-93-2. A skin photoirritation potential of PENNSAID® Topical Lotion

104-93-3. A modified Draize photosensitization study of PENNSAID® Topical Lotion

Phase 3

107-96. A double-blinded, placebo-controlled, three-way parallel clinical trial to confirm the safety and efficacy of PENNSAID® treatment and to compare two methods of measuring pain of the osteoarthritic knee

An overview of these studies is given in the following Table:

Protocol # Investigators	Completion Status (Start Date)	Design	Treatment Doses	Age Range (Mean)	M/F B/W/O	Treatment Duration
#100-89 Dr. H.I. Maibach	Complete (May 5, 1994)	Phase 1, Double-Blind, 4-way, Unicentered, Irritation and Sensitization Study.	Induction/Irritation: 0.2 mL of study product under occlusion, daily, Monday to Friday for 21 days Challenge: 0.2 mL of study product under occlusion, one application. Re-Challenge: 0.2 mL of study product under occlusion, one application. Provocative Use: 0.2mL offending preparation, twice daily non-occlusive, to cubital fossa, for 7 days.	25 - 78 (48.2)	13 / 12 0/16/9	Irritation - 21 days Sensitization - 5 - 15 days
#101-89-2 Dr. H.I. Maibach	Complete (February 26, 1996)	Phase 1, Double-Blind, 3-way, Unicentered, Sensitization Study.	Irritation/Induction: 0.2 mL of the 3 study preparations applied under occlusion. Applications repeated using same preparations on same sites, Monday, Wednesday, and Friday for 22 days, total of 9 applications. Challenge: 0.2 mL of each of the study preparations applied once under occlusion to new skin sites. Re-challenge: 0.2 mL of only the offending study preparations to newly randomly-allocated sites on back of subject, under occlusion once. Provocative Use: Twice daily non-occlusive applications of offending study preparation to cubital fossa, for 7 days.	17 - 83 (44.7)	119 / 104 68/91/64	Irritation - 22 days Sensitization - 5 - 16 days
#103-93-2 Dr. H.I. Maibach	Complete (March 28, 1996)	Phase 1, Double-Blind, 24-hour, Unicentered, 3-way, Photoirritation Study.	0.2. mL of each study preparation applied occluded to backs, upper arms or forearms.	23 - 77 (46.9)	13 / 12 0/14/11	24 hours
#104-93-3 Dr. H.I. Maibach	Complete (March 25, 1996)	Phase 1, Double-blind, 3-way, unicentered, photoirritation/ photo- sensitization study.	Photoirritation/Induction Phase: 0.2 mL of 3 study preparations applied under occlusion. Applications repeated 3 times weekly, using same preparations on same sites, (Monday to Wednesday) for 19 days, for total of 9 applications. Challenge: 0.2 mL of study preparations applied once under occlusion to duplicate new skin sites (i.e. 2 sites per lotion). Re-challenge: 0.2 mL of offending preparations applied once under occlusion to duplicate new skin sites (i.e. 2 sites per lotion). Provocative Use: Twice daily non-occlusive applications of offending study preparation to cubital fossa, for 7 days.	25 - 79 (58.5)	16 / 11 0/24/3	Photoirritation - 19 days Photosensitization - 5 - 19 days
#107-96	Complete (January 7, 1997)	Phase 3, Double-Blinded, Placebo Controlled, 3-arm Parallel Clinical Efficacy and Safety Trial of OA of the knee. 4 weeks	Treatment Phase: Subjects topically applied 1 ml of study preparations to 4 sites on knee (i.e. left side, right side, back side and front of knee), unoccluded, 4 times daily, for 4 weeks. Challenge: 10 drops (0.25 ml) applied once under occlusion to subject's forearm or back. Re-challenge: 10 drops (0.25 ml) applied once under occlusion to subject's forearm or back. Provocative Use: 10 drops (0.25 ml) applied (unoccluded) to cubital fossa, twice daily, for 7 days.	26 - 82 (61.8)	91 / 157 7/229/12	28 days

b(4)

The dermal safety study reports (100-89, 101-89-2, 103-93-2, 104-93-3) contain the disclaimer that they were not conducted in compliance with Good Clinical Practice (GCP) regulation, but done following "good scientific practices." The report for the phase 3 safety/efficacy study (107-96) does state that it was done in compliance with GCP.

I. STUDY 100-89. PRIMARY CUMULATIVE SKIN IRRITATION POTENTIAL OF PENNSAID® TOPICAL LOTION

Objective: To determine the cumulative skin irritation and skin sensitization potentials of PENNSAID on the skin of healthy human volunteers.

Design: Double-blind, single-center, 4-way, randomized, intraindividual study for irritation and sensitization in 25 healthy subjects (planned). Randomization was by site on the back of the subjects.

Comment *A sample size of 25 may be acceptable for irritancy testing, but not for sensitization potential. For testing sensitization potential, a sample size of at least 200 is recommended.*

- Testing Procedures. The study consisted of 3 periods after the initial screening visit to determine eligibility and obtain informed consent. In the **Irritation/Induction Phase** (Day 1-22), each subject received 0.2 mL application of each test drug (total of 4; see below) to the back with an occlusive system of a polypropylene chamber covered with paper or *Scanpor* tape (a patch) for 24 hours. The patch was removed the next day, followed by evaluation of the site and scoring. The same patches were repeated on the same sites daily (except for weekends, when they stayed for 72 hours) for 21 days, with a total of 15 applications and 15 evaluations. A 10-day **Rest Phase** ensued before challenge, potential rechallenge and provocative use tests (PUT). In the **Sensitization Test Phase**, each subject is ***challenged*** with reapplication of the test drugs over 4 new sites on the back, with patches in place for 48 hours, and evaluation at patch removal as well as 96 hours from the beginning of application. A test score of ≥1 would result in ***rechallenge*** with an identical procedure, whereas a test score of ≥1 at rechallenge would lead to the ***PUT***, which involved non-occlusive application of 0.2mL of test product twice daily for 7 days and evaluation on the 8th day. The report concedes that PUT was also performed in some subjects with a score of 0.5. If a skin score of ≥2 was observed, the skin site would be withdrawn from the study, and a score of 4 would be arbitrarily imputed for all remaining days of evaluation.

The composition of the test products is shown in the following Table:

	Composition of Test Products (% w/w)			
Ingredients	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Diclofenac sodium	1.5	0	0	10.0
Dimethyl Sulfoxide	45.5	45.5	4.55	45.5
Ethanol, ——				
Glycerin ——				
Propylene Glycol				
Purified Water				

b(4)

The rationale given in the report for Placebo-2 having a low concentration of DMSO is that its odor ensured blinding. A control with 10% diclofenac sodium was for "dose-ranging" for safety.

- Selection Criteria. Males or non-pregnant females, age ≥18 and in good general health, who signed informed consent. The following were exclusion criteria:

1. Significant skin disease such as acne, psoriasis or dermatitis
2. Participation in patch test panel within 30 days of study initiation
3. Use of topical or chronic systemic medications, including antihistamines and steroids
4. Dark skin (at Investigator's discretion) if deemed to interfere with grading
5. Allergy to diclofenac, aspirin or other NSAIDS

- Skin Evaluation. Scoring for the skin reactions used the following scale:

0	no visible reaction (negative)
0.5	equivocal response
1	erythema
2	erythema and induration
3	erythema, induration and vesicles
4	bullae

A positive skin sensitization reaction was determined by the development of erythema or worse (score ≥1) at the cubital fossa on the 8th day of PUT.

Results:

The study was conducted 5/5/94 to 6/21/94.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 25 ***subjects*** and 23 completed, 2 failed to come back for scheduled appointment during Irritation/Induction Phase (ID#s 13 and 25). For Sensitization Testing Phase, all 23 remaining subjects completed. Completion and discontinuation at ***application sites*** occurred as follows:

	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Completion	22	22	23	18*
Discontinuation	1	1	0	5*

*Since there were 7 subjects with discontinuation of application at the CONTROL site shown in subsequent Tables, (with actual Subject IDs), completion of application of the CONTROL test product could have occurred in only 16 subjects.

The subjects included 13 males and 12 females, and age ranged between 25 to 78 (mean 48). There were 16 Caucasians and 9 Hispanics.

- Irritancy Scoring:

Number of Subjects with Positive Scores in Irritation/Induction Phase (Total 23 Completers)

Worst Irritation Scores	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
0.5	4	4	1	2
1	3	1	1	0
2	0	0	0	1
3	0	0	0	0
4*	1	1	0	7

*As per protocol, a score of ≥2 required discontinuation at the test site and imputation of 4 for the rest of the study in that subject. The report also states that none had a real score of 4 showing bullae.

Comment *The above Table is based on Table 18 in the report (vol 8.11, page 180). However, in Table 20 (vol 8.11, page 182), which provides a subset analysis, PENNSAID sites showed 4 males and 2 females having had a score of 1 (3 subjects in Table 18). Such discrepancy needs to be clarified.*

The report has not presented a cumulative irritancy score for each test product. A comparison of the mean scores between PENNSAID and the Placebos was made.

	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Mean Scores ± SD	0.300 ± 0.764	0.158 ± 0.378	0.051 ± 0.172	Not Done

P-values (one-way ANOVA): PENNSAID vs Placebo-1=0.272, PENNSAID vs Placebo-2=0.057, Placebo-1 vs Placebo-2=0.406.

- Sensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID	PLACEBO-1	PLACEBO-2	CONTROL
Challenge	4/23	6/23	2/23	9/23
Rechallenge	3/6	1/4	0/3	3/9
PUT	0/4	0/2	0/0	0/3

Comments

1. The report states that despite being part of the protocol, there was no mention of rechallenge or PUT performed in the Sensitization Testing Phase (vol 8.11, page 161). However, the report also concedes that contrary to protocol, PUT was performed in some subjects with a score of 0.5 (vol 8.1, page 157). The section "Brief Summary of Adverse Events" agrees with the data in the above Table: "No subject (0.0%) had a positive formal skin sensitization assessment result after completing the PUT" (vol 8.11, page 170). Thus, there is contradictory information regarding the performance of rechallenge and PUT.

*2. It is also stated that records of dropouts were **not** kept in the CRFs.*

3. There were more subjects undergoing rechallenge than positive challenges (6 rechallenges with PENNSAID despite 4 positive challenges; 3 rechallenges with Placebo-2 despite 2 positive challenges). As well, there were more undergoing PUT than positive rechallenges (4 PUTs with PENNSAID despite 3 positive rechallenge; 2 PUTs with Placebo-1 despite 1 positive rechallenge). Since only scores of ≥1 led to rechallenge or PUT, there should always be fewer rechallenges and PUTs than positive challenges and positive rechallenges, respectively. A reverse finding suggests that in violation of the protocol, some subjects with negative scores went on to the next level of testing.

- Other Adverse Event Information: There were no deaths reported. Besides skin testing reactions and discontinuation due to the reactions, this report claims that there were no adverse events reported.

Comment *It is unusual that there were no adverse events other than the skin test reactions in a study of 25 subjects lasting for almost 7 weeks. There is a possibility of under-reporting.*

Conclusions:

The study report states:

> "Therefore, it can be seen that upon exposure to PENNSAID™ in this study, only 1 (4%) of 25 subjects required withdrawal due to adverse events, i.e., erythema and induration. This is the same as the number of subjects withdrawn from the Placebo-1 group. In light of this, it can be seen that PENNSAID™ is no more irritating than placebo. Also, throughout this study, only minor skin irritation was reported in subjects tested with PENNSAID ™, again, not significantly greater than placebo.
>
> "Further, no subject (0 (0.0%)) had a positive formal skin sensitization assessment result after completing the full sensitization testing."

Comments

1. The irritancy data appear to be similar between PENNSAID and Placebo-1, which is the vehicle minus diclofenac.

2. A small sensitization study with negative result from 23 subjects gives 95% confidence that the risk of sensitization is no higher than approximately 13%. Generally a larger sample size is needed for testing sensitization. The Applicant has conducted Study 101-89-2 to address this (see below).

3. Use of PUT data to define sensitization potential is not generally considered appropriate. In such testing, maximal provocation should be used to bring out the real potential of the product. The challenge and rechallenge data indicate that PENNSAID as well as the "control" with 10% diclofenac both gave positive reaction (challenge confirmed by rechallenge) in 3 out of 23 subjects, a rate of 13%. This needs to be confirmed with the larger sample size study, 101-89-2.

II. STUDY 101-89-2. SKIN SENSITIZATION STUDY OF PENNSAID® TOPICAL LOTION

Objective: To determine the cumulative skin irritation and skin sensitization potentials of PENNSAID on the skin of healthy human volunteers.

Design: Double-blind, single-center, 3-way, randomized, intraindividual study for irritation and sensitization in approximately 200 healthy subjects. Randomization was by site on the back of the subjects. The overall design is almost the same as that of 100-89. The following are key differences:

- This was a larger study with 200 healthy subjects planned (25 for 100-89).
- Only three of the four products used in 100-89 were tested. The "control" with high diclofenac concentration (10%) was removed. Placebos used in 101-89-2 were the same as those in 100-89, but termed differently: Placebo-H and Placebo-L (Placebo-1 and Placebo-2, respectively, in 100-89). Placebo-H is the vehicle of the PENNSAID product, while Placebo-L contains a reduced concentration of DMSO (4.55%, 1/10 the concentration in Placebo-H).
- The Irritation/Induction Phase in 101-89-2 consisted of 9 applications of 48 to 72 hours (week days 48, weekends 72), whereas in 100-89, it was with 15 daily applications of 24 hours (except weekends: 72 hours).
- The Rest Phase was 13 days in 101-89-2 (10 days in 100-89).
- Rechallenge evaluation for 101-89-2 was at 72 and 96 hours from time of patch application, due to the 48th hour falling on a Sunday. In 100-89, evaluation started at the 48th hour, upon patch removal.
- Added exclusion criteria in 101-89-2: females without negative pregnancy test or not using reliable contraception (such as tubal ligation, oral contraceptive, IUD, etc), history of renal, liver or peptic ulcer disorders, and nursing mothers. Females in 101-89-2 had to be postmenopausal for ≥1 year, be surgically sterile, or else practice an acceptable form of birth control, upon having normal menstrual period within 5 weeks, and negative pregnancy test within 1 week of product application.
- Test sites could be permanently discontinued from further application of patches if a skin score of ≥3 was attained (≥2 in 100-89).

Comments

1. A sample size of at least 200 subjects is appropriate.

2. The protocol states discontinuing application when a skin score of ≥2 was attained (vol 8.12, page 84). However, in the actual report, this cutoff became ≥3 (vol 8.12, page 32). As well, the report states that there were 9 applications in the Irritation/Induction Phase (vol 8.12, page 26) while the protocol required 10 applications over 22 days (vol 8.12, pages 84, 86 and 95) There does not seem to be documentation of protocol amendments addressing these changes. It is unclear which cutoff was actually followed in the study.

Results:

The study was conducted 2/26/96 to 4/16/96.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 223 ***subjects*** and 206 completed Irritation/Induction Phase, 17 failed to come back for scheduled appointment during this Phase. One subject discontinued after completion of the Irritation/Induction Phase for having "contracted cancer". For Sensitization Testing Phase, 204 of the 205

remaining subjects entered and completed (Subject #176 did not continue into this phase). Completion and discontinuation at ***application sites*** occurred as follows:

	PENNSAID	PLACEBO-H	PLACEBO-L
Completion	204	205	205
Discontinuation	19	18	18
• Poor tolerance	• 2	• 1	• 1
• Failure to return	• 17	• 17	• 17

The subjects included 119 males and 104 females, and age ranged between 17 to 83 (mean 45). There were 91 Caucasians, 68 Blacks, 53 Hispanics, 5 "Orientals", 5 "Asians" and 1 "NR".

- Irritancy Scoring:

Number of Subjects with Positive Scores in Irritation/Induction Phase (Total 206 Completers)

Worst Irritation Scores	PENNSAID	PLACEBO-H	PLACEBO-L
0.5	5	2	0
1	2	0	0
2	0	0	0
3	0	0	0
4*	2	1	1

*As per protocol, a score of ≥2 required discontinuation at the test site and imputation of 4 for the rest of the study in that subject. As stated above, the study report mentions discontinuing with a score of ≥3, and it is unclear which was followed. The report also states that none had a real score of 4 showing bullae.

Comment *The above Table is based on Table 18 in the report (vol 8.12, page 63). However, similar to the report on 100-89, such data are not consistent with those in Table 20 (vol 8.12, page 65), which would give the number of subjects showing a score of 0.5 with PENNSAID as 6, and a score of 1 with PENNSAID as 5.*

The report has not presented a cumulative irritancy score for each test product. A comparison of the mean scores between PENNSAID and the Placebos was made.

	PENNSAID	PLACEBO-H	PLACEBO-L
Mean Scores ± SD	0.030 ± 0.226	0.009 ± 0.091	0.005 ± 0.077

P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.105, PENNSAID vs Placebo-L=0.062, Placebo-H vs Placebo-L=0.805.

- Sensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID	PLACEBO-H	PLACEBO-L
Challenge	8/204	5/206	1/205
Rechallenge	5/8	3/5	0/1
PUT	2/5	0/3	0/0

- Other Adverse Event Information: One case of death due to cancer was reported. This subject (#103) was a 45-year-old male Caucasian, who completed the Irritation/Induction Phase. The CRF has no details on the cancer or death. It is noted that the reasons for dropout in this subject are internally not consistent in the CRF. In one place, (vol 8.12, page 213E), the dropout is stated to be for "personal reason". In the "Adverse Drug Reaction Form", the discontinuation is due to:

"Patient contracted cancer and could not continue, died."

The date for the adverse reaction has been crossed out and replaced with "dropout 3-25-96" and the description was "Cancer - leading to death".

Besides skin testing reactions and discontinuation due to the reactions, this report claims that there were no adverse events reported.

Comments

1. It appears unusual that Subject #103 could complete the Irritation/Induction Phase and died of cancer before the Sensitization Testing Phase. It is more likely that Subject #103 discontinued due to serious adverse event (cancer), rather than death during the study period. The circumstances surrounding this adverse event are not clear, and it is important that the Applicant provide more details.
2. It is also unusual that there were no adverse events other than the skin test reactions in a study of 223 subjects lasting for almost 7 weeks. There is a possibility of under-reporting.

Conclusions:

The study report states:

> "Therefore, it can be seen that upon exposure to PENNSAID™ in this study, only 1 (4%) of 25 subjects required withdrawal due to adverse events, i.e., erythema and induration. This is the same as the number of subjects withdrawn from the Placebo-H group. In light of this, it can be seen that PENNSAID™ is no more irritating than placebo. Also, throughout this study, only minor skin irritation was reported in subjects tested with PENNSAID™, again, not significantly greater than placebo.
>
> "Two subjects (2 (0.98%)) had a positive formal skin sensitization assessment result after completing the full sensitization testing."

Comments

1. The conclusion that 1 (4%) of 25 subjects exposed to PENNSAID withdrew due to adverse events, i.e. erythema and induration, is not supported by the data in this study. It appears to be an error due to copying from the conclusion for the Clinical Study Report for Protocol 100-89. The data do suggest that PENNSAID is somewhat greater in irritancy potential than its vehicle (PENNSAID: 7 subjects with score of ≤1 and 2 discontinuations due to score of ≥2; Placebo-H: 2 with score of 0.5 and 1 discontinuation due to score of ≥2)
2. Use of PUT data to define sensitization potential is not generally considered appropriate. In such testing, maximal provocation should be used to bring out the real potential of the product. The challenge and rechallenge data indicate that both PENNSAID and the vehicle containing DMSO, "Placebo-H", gave positive sensitization reactions (challenge confirmed by rechallenge): 5/204 (2.45%) for PENNSAID and 3/206 (1.46%) for vehicle. These low rates suggest low sensitization potential of PENNSAID, but above that of its vehicle containing 45.5% DMSO.

III. STUDY ~~103-93~~-2. A SKIN PHOTOIRRITATION POTENTIAL OF PENNSAID® TOPICAL LOTION

Objective: To determine the photoirritation potentials of PENNSAID on healthy human skin.

Design: Double-blind, single-center, 3-way, randomized, intraindividual study for photoirritation in 25 healthy subjects (planned).

The study consisted of a **Pre-Treatment Screening Visit** and the **Photoirritation Testing**. At the screening, the subjects gave informed consent and underwent inclusion/exclusion interview and medical assessment. The subject's MED (minimal erythema dose) was determined by irradiation of 3 skin sites with different doses of unfiltered light from an air-cooled Kromayer lamp (UV-A and UV-B).

- Testing Procedures. Randomization of test products for application was by site. All subjects were treated with PENNSAID, Placebo-H and Placebo-L (see Protocol 101-89-2). Before application, the skin was stripped with cellophane tape until it glistened. Then 0.2 mL of test product was applied to the back, upper arm or forearm and left to dry for 10 minutes. Irradiation was then done with a Woods Light Inspecto Lamp (non-erythematous UV-A light of 320-450 nm) for 45 minutes at a distance of 9 inches. The sites were then exposed to 2/3 of an MED from an air-colled Kronmayer Lamp that gives both non-erythematous and erythematous light (UV-B of 285-350 nm). These sites were occluded for 24 hours and then examined for acute photoirritation. The skin reaction was graded with a scale used in Protocols 100-89 and 101-89-2 by a blinded evaluator.

Comments

1. The Applicant has not presented a rationale in conducting photoirritation and photosensitization studies. If there is no absorption in the UV-B, UV-A or visible spectrum by any ingredient of the drug product, these tests would not be necessary.
2. The amount of energy used to determine MED and administered from the Woods Light Inspecto Lamp has not been presented in the protocol or the study report.
3. It is unclear whether the test sites were actually unoccluded or occluded for 24 hours. The protocol requires occlusion (vol 8.13, pages 8 and 20). The report states that there was a protocol deviation and the sites were not occluded (vol 8.12, page 251). Yet, there are other places that mention occlusion. To be even more confusing, within the same Table (Table #5, vol 8.12, page 242), there is conflicting information: "unoccluded" under "Dosing Schedule" and under "Route and Mode of Administration" for Placebo-L, whereas for PENNSAID and Placebo-H, "Route and Mode of Administration" was "occluded".
4. There is no mention of non-irradiated controls for comparison in case the tests were positive.
5. The use of celluphane stripping for photoirritation testing is not conventional. No rationale has been offered. Stripping may be used to potentiate the effect of photoirritation. However, for a 24-hour application, there is the possibility of reduced skin exposure due to enhanced systemic absorption after the stripping.
6. A sample size of 25 is acceptable.

- Selection Criteria. These were virtually identical to those of Protocol 101-89-2, except that the requirement for normal menstrual period within 35 days of product application was not in Protocol 103-93-2.

- Skin Evaluation. Scoring for the skin reactions used the following scale:

0	no visible reaction (negative)
0.5	equivocal response
1	erythema
2	erythema and induration
3	erythema, induration and vesicles
4	erythema, induration and bullae

Results:

The study was conducted 3/28/96 to 3/29/96.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 25 ***subjects*** and all completed study.

The subjects included 13 males and 12 females, and age ranged between 23 to 77 (mean 47). There were 14 Caucasians, 9 Hispanics, 1 "Oriental", and 1 "Indian".

- Photoirritaion Scoring: No positive reactions were observed in any subject for any test product.

- Other Adverse Event Information: This report claims that there were no adverse events reported.

Comment *It may not be unusual that there were no adverse events in a 24-hour study.*

Conclusion:

The study report states:

> "Therefore, there is no risk of photoirritation with the use of PENSSAID™."

Comment *The conclusion of no risk is not warranted. A small study with negative result from 25 subjects gives 95% confidence that the risk of photoirritation is no higher than approximately 12%.*

IV. STUDY 104-93-3. A MODIFIED DRAIZE PHOTOSENSITIZATION STUDY OF PENNSAID® TOPICAL LOTION

Objective: To determine the cumulative skin photoirritation and photosensitization potentials of PENNSAID on the skin of healthy human volunteers.

Design: Double-blind, single-center, 3-way, randomized, intraindividual study for photoirritation and photosensitization in a minimum of 25 healthy subjects.

- Testing Procedures. The study consisted of a **Pre-Treatment Screening Visit, Photoirritation/Induction Phase,** and the **Photosensitization Testing Phase**. At the screening, the subjects gave informed consent and underwent inclusion/exclusion interview and medical assessment. All subjects were treated with PENNSAID, Placebo-H and Placebo-L (see Protocol 101-89-2). However, the terms Placebo-1 and Placebo-2 were also used interchangeably with Placebo-H and Placebo-L, respectively.

The Photoirritation/Induction Phase (Days 1-19) followed screening immediately. The subject's MED (minimal erythema dose) was determined by irradiation of 3 skin sites with different doses of unfiltered light from an air-cooled Kromayer lamp (UV-A and UV-B). After determining MED, during the first treatment visit (Day 1, Monday), 0.2 mL of each test product was applied to the back using an occlusive system of a polypropylene chamber covered with *Seanpor* tape (a patch), to be left for 24 hours. The randomization was by application site. On the second day, the subject returns for patch removal and scoring. The sites were then irradiated with 1 MED of unfiltered light from an air-cooled Kromayer light (UV-A and UV-B light) followed by irradiation with 10 MEDs of window glass filtered non-erythematous light (UV-A). Another patch with the same product was applied to the same site for each of the sites. These procedures were repeated on the third day. On the fourth day, the sites were evaluated and irradiated without patch removal. The fifth day involved repeat evaluation and

leaving the patches in place over the weekend. The same procedures were repeated in the second and third weeks, for a total of 9 applications and 14 evaluations.

The Photosensitization Testing Phase (Days 29-47) occurred after a 9-day rest period with no applications or evaluations (Day 20-28). Challenge (Days 29-33) started with application of 0.2 mL of study product under occlusion to new duplicate skin sites. After 24 hours, the patch on the right was removed, and the site evaluated and irradiated with 2/3 MED from a Kronmayer lamp (UV-A and UV-B light) followed by 10 MEDs of window glass-filtered light. This site was left uncovered. The patch on the left side was removed after an additional 48 hours, and then both right and left patch sites evaluated. They were again evaluated after another 24 hours (Day 33). If there was persistent erythema (score of ≥1), rechallenge (Days 36-40) took place at new sites with the same procedure for the offending product, after two days of rest (Days 34-35). Positive finding (score of ≥1; sometimes ≥0.5) would lead to PUT (Days 40-47), which consisted of non-occlusive application of 0.2 mL of study product to cubital fossa twice daily for 7 days and evaluation on the 8th day.

Comments

1. The Applicant has not presented a rationale in conducting photoirritation and photosensitization studies. If there is no absorption in the UV-B, UV-A or visible spectrum by any ingredient of the drug product, these tests would not be necessary.

2. The Photoirritation/Induction Phase did not include non-irradiated controls. This may make interpretation of positive photoirritation reactions difficult.

3. The sample size of 25 minimum is low but consistent with common practice. A larger sample size would be more desirable, as this would give a better risk estimate.

4. Use of both UV-B and UV-A in testing is appropriate. However, using PUT data to define photosensitization potential is not generally considered appropriate. In such testing, maximal provocation should be used to bring out the real potential of the product.

- Selection Criteria. These were the same as those of Protocol 101-89-2.

- Skin Evaluation. Scoring for the skin reactions used almost the same scale as that in Protocol 103-93-2, with the addition of a letter grade "G", which stands for minimal glazing, such as in the "peau d'orange". However, the report also concedes that "this was not used as a score."

Results:

The study was conducted 3/25/96 to 5/10/96.

- Investigator: H.I. Maibach, M.D., Skin Sensitivity Center, 2435 Ocean Ave, San Francisco, CA 94127

- Subject Disposition and Demographics: Enrolled 27 ***subjects*** and all completed the study, except that rechallenge was not completed for subject #27 due to an error of the site administration.

The subjects included 16 males and 11 females, and age ranged between 25 to 79 (mean 59). There were 24 Caucasians and 3 Hispanics.

- Photoirritancy Scoring:

Number of Subjects with Positive Scores in Photoirritation/Induction Phase (Total 27 Completers)

Worst Irritation Scores	PENNSAID	PLACEBO-H	PLACEBO-L
0.5	4	5	3
1	2	0	0
2	0	0	0
3	0	0	0
4	0	0	0

The findings presented in this Table (given in Table #18 and in the Synopsis) are not consistent with those in Table #19, which provides subset breakdown with age and sex. From Table 19, the number of subjects giving a score of 0.5 was 2 for PENNSAID, 2 for Placebo-H and 1 for Placebo-L; there was only one subject with a score of 1 (PENNSAID).

A comparison of the mean scores between PENNSAID and the Placebos was made in the report:

	PENNSAID	PLACEBO-H	PLACEBO-L
Mean Scores ± SD	0.042 ± 0.109	0.040 ± 0.123	0.017 ± 0.069

P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.873, PENNSAID vs Placebo-L=0.113, Placebo-H vs Placebo-L=0.153.

- Photosensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID	PLACEBO-H	PLACEBO-L
Challenge (non-irradiated)	8/27	6/27	2/27
Challenge (irradiated)	7/27	5/27	2/27
Rechallenge (non-irradiated)	5/8	3/6	1/3
Rechallenge (irradiated)	5/8	3/5	1/3
PUT	0/6	0/4	0/2

Comments

1. In the rechallenge for PENNSAID, Subject #13 gave both positive and negative results at the irradiated site (Table #20, vol 8.13, page 164). This must be an error.

2. The data indicate that the rates of positive reactions at the irradiated and non-irradiated sites were similar, both for the challenge and for the rechallenge tests. The most likely explanation is that these were not photosensitization reactions, but rather evidence of sensitization. These data would have made PUT unnecessary. Moreover, use of PUT data is not generally considered appropriate, as maximal provocation is used to bring out the real potential of the product. In this case, more intense testing has not established the photosensitization potential of PENNSAID.

3. The Investigator had performed rechallenges in some situations without a prior positive challenge. These extra rechallenges were due to positive reactions on the non-irradiated challenge sites, and were thus attempts to clarify their meaning. In one instance (Subject #2 with PENNSAID), the rechallenge turned out to be negative, and in another (Subject #22 with Placebo-L), rechallenge gave positive result and led to PUT.

- Other Adverse Event Information: Besides skin testing reactions, this report claims that there were no adverse events reported.

Comment *It is unusual that there were no adverse events other than the skin test reactions in a study of 27 subjects lasting for almost 7 weeks. There is a possibility of under-reporting.*

Conclusions:

The study report states:

> "The skin photoirritation and sensitization/photosensitization potentials of PENNSAID™ were demonstrated to be minimal. ..... Throughout this study, only minor skin irritation was reported in subjects tested with PENNSAID™, not significantly greater than placebo. ..... the minor skin photoirritation and sensitization/photosensitization of PENNSAID™ seems to be an acceptable, low –level risk."

Comments

1. The data indicate that the rates of positive reactions at the irradiated and non-irradiated sites were similar, both for the challenge and for the rechallenge tests. Even without PUT, the more intense testing with occluded challenge and rechallenge has not established the photosensitization potential of PENNSAID. The data are consistent with sensitization rather than photosensitization. However, the rates observed in this study are higher than those seen in 101-89-2: 5/27 (18.52%) for PENNSAID and 3/27 (11.11%) for vehicle (2.45% and 1.46%, respectively, in 101-89-2).

2. A small photosensitization study with negative result from 27 subjects gives 95% confidence that the risk is no higher than approximately 11%.

V. STUDY 107-96. A DOUBLE-BLINDED, PLACEBO-CONTROLLED, THREE-WAY PARALLEL CLINICAL TRIAL TO CONFIRM THE SAFETY AND EFFICACY OF PENNSAID® TREATMENT AND TO COMPARE TWO METHODS OF MEASURING PAIN OF THE OSTEOARTHRITIC KNEE

This is a safety/efficacy study and the study report involves 8 volumes of the submission (vol 8.14 to 8.21), but only vol 8.14 is provided for consultation. The other volumes, which include the references and all appendices, are not part of this review. The protocol and amendments are within the appendices. This consult focuses on the dermal safety data in this study and the sensitization testing.

Objective: To confirm the safety and efficacy of PENNSAID™ in the symptomatic treatment of osteoarthritis of the knee (primary) and to validate the accuracy of Dimethaid's method used to measure osteoarthritic knee pain in clinical trial (secondary)

Comment *The testing for sensitization is not an explicitly stated objective of this study.*

Design: Double-blind, multi-center, 3-arm, randomized, parallel-group study of 150 subjects (planned) with 3 phases: screening visit, treatment phase and sensitization testing phase.

- Study Procedures.

Screening. Patients with suspected osteoarthrits were screened, gave informed consent and underwent inclusion/exclusion interview, medical assessment and knee x-ray (if not taken in last 6 months). Blood and urine were submitted to a pre-designated laboratory for analysis. Patients meeting all entry criteria went through a washout period for narcotic analgesics, oral NSAIDs and other topical arthritic products and related pain-management products for one week. Use of acetaminophen (650 mg four times a day as needed) was allowed, except during the 24 hours prior to baseline WOMAC (Western Ontario MacMaster osteoarthritis questionnaire) assessment.

Treatment Phase (Visit 1 to Visit 5). During this phase, patients were treated as randomized. They were randomized to PENNSAID, "Control" or "Placebo" Each patient was given a bottle of study lotion and instructions for application, using 1 mL (40 drops) per knee four times a day. The use of acetaminophen tablets (325 mg) up to 12 tablets per day was allowed. Starting from Visit 2, signs of skin irritation and the degree of irritation were recorded. Blood and urine sampling were repeated at Visit 5, the final treatment phase visit.

Comment *The compositions of the "Control" and "Placebo" in this study are the same as those of the "Placebo-1" and "Placebo-2", respectively, in Protocol 100-89, and of "Placebo-H" and "Placebo-L", respectively, in Protocols 101-89-2 and 103-93-2.*

Sensitization Testing Phase. For the first 145 patients completing Visit 5, skin sensitization testing was conducted 2 to 4 weeks after the end of treatment, based on the procedures of "challenge", "rechallenge" and "PUT" in Protocol 101-89-2. Challenge was with 10 drops (0.25 mL) of the patient's study lotion on a cotton plug in a plastic chamber, inverting the chamber and taping it to skin (forearm or back) for 48 hours. The Investigator would phone the patient to remove the chamber and describe the degree of irritation observed. After another 48 hours, the patient returned for final evaluation of irritation. If the test site showed erythema (score of ≥1), rechallenge with the same procedure was carried out at a new site. If after 96 hours, erythema was also observed, the patient underwent PUT, which involved non-occlusive application of 10 drops of study lotion to cubital fossa twice a day for one week. A positive sensitization response was defined by a score of ≥1 (erythema) after one week of such application.

Comment *In this study, there was no proper induction phase, and the treatment phase acted for the induction phase of a formal testing. As well, use of PUT data to define sensitization is not generally considered appropriate, and maximal provocation is usually used to bring out the real potential of the product. Thus, the design of this study was not adequate to determine sensitization. However, if positive reactions develop with challenge and rechallenge despite suboptimal induction, the data could be supportive of sensitization observed in healthy subjects in the phase 1 studies.*

- Selection Criteria. Patient with osteoarthritis fitting certain radiologic and clinical criteria were enrolled if between the ages of 18 and 80 and in reasonably good health, having blood and urine test results within acceptable ranges at screening. Females had to be (a) surgically sterile or postmenopausal for at least 1 year, or (b) not pregnant (normal menstrual period within 35 days of entry and negative pregnancy test within 48 hours of entry), and using acceptable contraception, including oral contraceptives, IUD, spermicide with barrier method, or surgically sterile male partner). Exclusion criteria were:

1. known hypersensitivity or contraindications to the use of diclofenac, DMSO, glycerine, propylene glycol, alcohol, ASA or other NSAID
2. clinically active renal, liver or peptic ulcer disease
3. history of alcohol or drug abuse within 1 year of entry
4. lactation
5. psoriasis (at site of application), syphilitic neuropathy, ochronosis, metabolic bone disease (except osteoporosis or Paget's disease of other than the affected knee) or acute trauma
6. requirement for oral corticosteroids, having received intraarticular steroid injection within 60 days of entry or requiring topical corticosteroid at the site of application

Additional entry requirements included:

- selection consistent with all warnings, precautions and contraindications in the label for oral diclofenac

- discontinued ≥1 week before entry: (a) all oral NSAIDs including OTC ASA and ibuprofen (acetaminophen allowed until 24 hours before first treatment visit), (b) topical products including methyl salicylate, camphor, menthol, capsicum, and OTC analgesics, and (c) glucosamine

• Evaluation Criteria. The evaluations for efficacy will not be addressed in this consult.

Safety evaluation included information from patient diary and case report form's adverse event reporting. The study coordinator asked about specific adverse events from a checklist, and offered a subjective opinion whether an adverse event has occurred. ***An event was not considered to be related to application of the lotion if the event occurred in a similar number of patients in each treatment group.*** Events considered related to study drug application included those that occurred at the site of application and events related to the characteristic garlic odor associated with the use of DMSO.

Skin irritation scoring was according to the following scale:

0	no visible reaction or equivocal response (questionable reaction)
0.5	itching sensation
1	erythema (redness)
2	erythema with induration (i.e., swelling)
3	erythema with induration and vesiculation (small blisters <5 mm)
4	erythema with induration and bullae (large blisters > 5 mm)

The criterion for sensitization was the development of erythema (score of ≥1) at the end of PUT.

Comment *The definition of "relatedness" of an adverse event to study drug involves a post-hoc examination of whether the number of cases in the treatment group stands out. This is in contrast to a determination by the Investigator with considerations based on his/her experience and the pharmacology of the drug. Thus, caution should be exercised in interpreting the data regarding "relatedness". As discussed above,, use of PUT data is not optimal in determining sensitization, as maximal provocation is generally used to bring out the real potential of the product.*

• Significant Protocol Changes relating to Dermal Safety Evaluation. There are several changes to be noted:

- The terminology used for the scoring system for irritation/sensitization reactions was clarified. (Nov 6, 1996)
- Sensitization testing schedule amended to "more closely reflect standard procedures. Due to blinding issues, all patients were to be tested for sensitization." (Nov 6, 1996)
- During the time interval (2-4 weeks) between the Treatment Phase and the Sensitization Testing Phase, patients were told to only take acetaminophen for pain relief in order to avoid the use of NSAIDs. (Feb 17, 1997)
- Patients with psoriasis, but ***not*** at the site of application, could be included (Criterion #5 had prevented enrollment) (Feb 17, 1997)
- If a patient developed skin irritation that was evaluated at a score of 3 or 4, the investigator was asked to discontinue treatment, and to ensure that patients did not continue to apply the lotion to skin that was irritated to this level. (Feb 17, 1997)

Results:

The study was conducted 1/7/97 to July, 1997.

Comment *A specific date of completion of this study cannot be found in the material provided. It is noted that substantive protocol amendments were developed as late as in May, 1997. According to Section 9.8 of the report (vol 8.14, pages 56 to 60), there was also an amendment on November 6, 1997, which could be a*

typographic error. It is difficult to conceive of the impact of the late protocol changes on the conduct of the study; it appears that the Investigators would be following different procedures at different times of the study.

- Investigators:

b(4)

Comments

1. Although this is a multi-center trial, it actually covers a relatively small geographic region in Southern Ontario, Canada. The applicability of the clinical study data to the diverse population in the United States should be addressed by the Applicant.

2. The qualifications of the Investigators have not been included in this consult and therefore not reviewed.

- Subject Disposition and Demographics: Randomized 267 patients, and 248 received one of the three treatments (PENNSAID 84, Control 80, and Placebo 84), with 209 completing the Treatment Phase (PENNSAID 74, Control 66, and Placebo 69). The withdrawals are shown as follows:

	PENNSAID	Control	Placebo
Total Withdrawal	10	14	15
Reasons*:			
• Lack of efficacy	2	9	9
• Poor tolerance to test drug	5	5	1
• Failure to appear for scheduled appt	0	2	2
• Insufficient/unreliable patient cooperation	0	3	1
• Protocol violation	1	0	4
• Other – medical reason	1	0	4
• Other – non-medical reason	0	1	1

*Withdrawal could be due to more than one reason in a patient.

Comment *This Table shows "Poor Tolerance to Study Medication" leading to discontinuation in 11 patients (PENNSAID 5, Control 5 and Placebo1). However, the safety conclusion section (Section 13; vol 8.14, page 215) states that only 2 patients given PENNSAID, 3 given control and none given placebo dropped out for this reason. The discrepancy is unexplained.*

For Sensitization Testing Phase, 145 patients participated (PENNSAID 53, Control 47, and Placebo 45), and 139 completed (PENNSAID 49, Control 46, and Placebo 44). The 6 withdrawals in this phase were either due to "insufficient and/or unreliable patient" (PENNSAID 1 and Control1), or "protocol violation (Investigator error)" (PENNSAID 3 and Placebo 1).

The demographic data of the enrolled patients showed:

	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
Age (Mean ± SD)	62.5 ± 11.7	62.1 ± 11.4	60.8 ± 11.4
Males	32	26	33
Females	52	54	51
White	79	74	76
Black	1	3	3
Asian	4	3	5

- Irritancy Scoring during Treatment Phase:

Scores in Irritation Assessment in Treatment Phase

Worst Irritation Scores	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
0	72	75	83
0.5	3	1	1
1	7	4	0
2	1	0	0
3	1	0	0
4	0	0	0

- Results of Sensitization Testing:

Positive Challenge, Rechallenge, and PUT

Test	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
Challenge	16/49	9/46	0/44
Rechallenge	12/16	7/9	0/0
PUT	0/12	1/7	0/0

- Adverse Event Reporting: Few adverse events were considered "related". The following have been reported:

"Related" Adverse Events Not Classified under Skin & Appendages in Study 107-96 (From Table #82 pp 153-4)

	PENNSAID (N=84)	Control (N=80)	Placebo (N=84)
Body odor	2 (2.38%)	0	0
Halitosis	4 (4.76%)	1 (1.25%)	0
Vasodilation at application site	0	1 (1.25%)	0
Taste perversion	4 (4.76%)	3 (3.75%)	4 (4.76%)
Paresthesia at application site	12 (14.29%)	18 (22.50%)	5 (5.95%)

Adverse Events Classified under Skin & Appendages in Study 107-96 (From Table #82 pp 153-4)

	PENNSAID (N=84)		Control (N=80)		Placebo (N=84)	
	"Related"	"Not Related"	"Related"	"Not Related"	"Related"	"Not Related"
Dry skin	0	0	0	0	0	1 (1%)
Dry skin at application site	30 (36%)	0	11 (14%)	0	1 (1%)	0
Herpes simplex	0	0	0	0	0	1 (1%)
Pruritus	0	2 (2%)	0	5 (6%)	0	1 (1%)
Pruritus at application site	9 (11%)	0	6 (8%)	0	3 (4%)	0
Rash	0	3 (4%)	0	2 (3%)	0	2 (2%)
Rash at application site	11 (13%)	0	6 (8%)	0	3 (4%)	0
Sweating	0	0	0	1 (1%)	0	0
Urticaria	0	1 (1%)	0	1 (1%)	0	0
Vesiculobullous rash	1 (1%)	0	0	0	0	0

There were 52.4% (44/84) patients in the PENNSAID arm who had "related" adverse events reported. However, only 24 of these patients (28.6%) had documentation in the diary.

Comment

1. The Applicant argues that the reporting rate for "related" adverse events of 52.4% is exaggerated, as it includes a large number of cases with minor dry skin at the application site thought to be not significant by the

patient, and thus not recorded in diary. The diary entry sheet has this reminder for each day: "Please record any abnormal event you think may be related to the use of the study medication that happened during the last 24 hours." The Applicant asserts that -

> *"... an adverse event is something experienced by the patient and most accurately reported by that patient, not by an outside observer and that the diary reports, with a frequency of 28.6%, be accepted as the most reasonable and correct estimate of skin-related adverse events."*

As discussed above, the definition of "relatedness" by the Applicant is questionable. Here the Applicant advocates that patient reporting should be considered most accurate and a lower rate of "related" adverse events be accepted on the basis of diary entries. While it is reasonable that an adverse event should be a finding that has occurred in the patient, not all adverse events are experienced (e.g., cancer, internal congenital anomaly, laboratory abnormality). In this study, the study coordinator asked about specific adverse events from a checklist, and this is a more sensitive technique than the patient diary in soliciting events "experienced" by the patient. An examination of the reported items shows that all of them which were reported by the 44 patients (52.4%) could have been subjectively experienced, not just observed by the study coordinator.

2. Many cases of "dry skin" actually involved reporting of peeling, scaling and flakiness (Table #310; vol 8.14, pages 421-432). Use of the term "dry skin" may be confusing.

Deaths, Serious Adverse Events and Other Significant Adverse Events. No deaths were reported in this study. Serious adverse events and other significant adverse events are listed in Tables #311 and #312 (vol 8.14, pages 434-440). There were two serious adverse events: aphasia/confusion secondary to cerebrovascular accident (#1032; 74 year old female) and arrhythmia (#4023; 66 year-old male). Both were on PENNSAID, and in the former case, treatment was discontinued. Other significant adverse events can be summarized in the following Table:

Patient ID	Age	Sex	Adverse Event	Test Drug /Discontinuation?
1039	76	F	Pruritus/headache	Control/yes
1040	72	F	Rash/pruritus	PENNSAID/yes
1046	37	F	Pain/back pain	Placebo/yes
1054	71	F	Arthralgia	PENNSAID/yes
1065	71	M	Arthralgia/paresthesia	Control/yes
1069	74	M	Asthenia/palpitation	PENNSAID/yes
1077	46	F	Rash/pruritus/vesiculobullous rash	PENNSAID/yes
3012	68	M	Arthralgia/ headache	Placebo/yes
4011	72	F	Backpain/arthralgia	Placebo/yes
4010	50	F	Pharyngitis/ear infection	Placebo/yes
4031	59	F	Rash/arthrosis/face edema/dyspepsia/headache/malaise	PENNSAID/yes
5008	54	F	Arthrosis	Placebo/yes
5010	65	F	Paresthesia/dry skin	Control/yes
5012	60	M	arthrosis	Placebo/yes
6006	48	M	Pruritus/arthralgia	PENNSAID/yes
6014	58	M	Body odor/halitosis	PENNSAID/yes
6018	69	F	Peipheral edema	Control/yes
6024	69	F	Arthrosis/headache/taste perversion	Control/yes

- Clinical Laboratory Testing. The only clinical laboratory test that showed significant differences in abnormal findings between treatment arms was alanine aminotransferase (ALT/SGPT). A greater number of patients treated with control lotion (4) had changes from normal to abnormal than in other groups (1 with PENNSAID and 0 with Placebo):

Changes in ALT Levels from Normal to Outside Normal Range in Study 107-96

	PENNSAID	Control			
Patient ID	4040	1048	3011	3034	4025
Pre level	34	24	33	36	54
Post level	130	88	54	46	58
Normal	<55	<55	<42	<42	<55

Comments *The changes in Patients #4040 and #1048 were 3 fold or higher above baseline, although they were within 3x upper limit of normal range. The changes in these two patients were also accompanied by substantial changes in AST/SGOT (from 32 to 85 in #4040, and from 29 to 101 in #1048; normal <45 in both laboratories). Although diclofenac use may be associated with liver enzyme changes, DMSO is believed to be protective against liver toxicity induced by some hepatotoxins. Without details on the systemic availability of these components upon topical use, it is difficult to interpret the data from these two cases. Transaminase elevation due to topical use of diclofenac has neither been ruled in or ruled out.*

Conclusions:

The study report states:

> "Other than minor local skin irritation, no significant safety issues were identified in this study. ..... data suggest a minor, local irritation by the 45% DMSO which is common to only the PENNSAID™ and control study lotions; this observation is neither new, surprising or of great clinical significance. If 2.4% (2/84) of patients, for whom PENNSAID™ will be prescribed, discontinue to the lotion, this would not be an excessive or unusual rate for any drug." (vol 8.14. page 215)

Comments

1. This study was not properly designed to determine sensitization potential. PUT is not an adequate methodology for this purpose, and patients did not undergo appropriate induction. Despite this, 12/49 (24.5%) patients treated with PENNSAID and 7/46 (15.2%) with its vehicle containing DMSO had positive reaction upon rechallenge. Although DMSO in the vehicle is an irritant, the additional reactions observed with PENNSAID rechallenge are consistent with data from the phase 1 studies. As a preparation containing diclofenac but not DMSO has not been tested, it is not possible to distinguish between irritation and sensitization from this testing.

2. It appears to be inaccurate to state that only 2/84 patients given PENNSAID discontinued due to the treatment. Although the Applicant dismisses 2 cases of pruritus and 3 cases of rash as being "not related", at least 5 patients who discontinued PENNSAID had adverse events that could be due to the treatment:

#1040 Rash/pruritus
#1077 Rash/pruritus/vesiculobullous rash
#4031 Rash/arthrosis/face edema/dyspepsia/headache/malaise
#6006 Pruritus/arthralgia
#6014 Body odor/halitosis

3. Desquamation, variably described as peeling, scaling, and flaking, but coded as "dry skin" in this report, is a prominent adverse event (36% PENNSAID patients and 14% control patients). However, this event was minimized by the Applicant as being "minor". Paresthesia, rash, and pruritus at the application site, as well as halitosis and body odor were the other "related" adverse events in patients treated with PENNSAID.

4. Systemic availability and internal organ toxicity cannot be determined by this study. Although the cause of transaminase elevation in a patient treated with PENNSAID in this study cannot be determined, it is known that diclofenac used orally may be associated with liver toxicity. Enzyme elevation has been observed in 4% of 3700 patients treated in a large trial for 2 to 6 months (Voltaren label).

Summary and Conclusions

This NDA presents an NSAID, diclofenac, in a solution containing DMSO (PENNSAID Solution) for the treatment of osteoarthritis.

Five studies have been reviewed in this consult: four phase 1 dermal safety studies and one phase 3 trial on the safety and efficacy of PENNSAID Lotion in the treatment of osteoarthritis, with sensitization testing in a subset of patients after the treatment period. The phase 1 studies examined the potential of PENNSAID Lotion for irritancy, contact sensitization, photoirritation, and photoallergenicity. In each of the five studies, in addition to the PENNSAID Lotion, two other test products were applied: Placebo-H (Placebo-1), which was the vehicle lotion without diclofenac, and Placebo-L (Placebo2), a vehicle containing a low strength of DMSO (1/10 of the concentration in PENNSAID or in Placebo-H). The studies were:

Phase 1
100-89. Primary cumulative skin irritation potential of PENNSAID® Topical Lotion
101-89-2. Skin sensitization study of PENNSAID® Topical Lotion
103-93-2. A skin photoirritation potential of PENNSAID® Topical Lotion
104-93-3. A modified Draize photosensitization study of PENNSAID® Topical Lotion
Phase 3
107-96. A double-blinded, placebo-controlled, three-way parallel clinical trial to confirm the safety and efficacy of PENNSAID® treatment and to compare two methods of measuring pain of the osteoarthritic knee

The results of the studies can be summarized in the following Tables. Data from Study 103-93-2 are not shown, as there were no positive reactions in photoirritation testing.

Mean Irritancy Scores in the Induction Phase

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89 (N=23)	0.300 ± 0.764	0.158 ± 0.378	0.051 ± 0.172
	P-values (one-way ANOVA): PENNSAID vs Placebo-1=0.272, PENNSAID vs Placebo-2=0.057, Placebo-1 vs Placebo-2=0.406.		
101-89-2 (N=206)	0.030 ± 0.226	0.009 ± 0.091	0.005 ± 0.077
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.105, PENNSAID vs Placebo-L=0.062, Placebo-H vs Placebo-L=0.805.		
103-93-2 (N=27)	0.042 ± 0.109	0.040 ± 0.123	0.017 ± 0.069
	P-values (one-way ANOVA): PENNSAID vs Placebo-H=0.873, PENNSAID vs Placebo-L=0.113, Placebo-H vs Placebo-L=0.153.		
107-96	Safety and efficacy study with no induction phase		

Positive Challenge and Rechallenge Rates

	PENNSAID	Placebo-1 (Placebo-H)	Placebo-2 (Placebo-L)
100-89			
Challenge	4/23	6/23	2/23
Rechallenge	3/6	1/4	0/3
(% positive)*	(13.0%)	(4.3%)	(0)
101-89-2			
Challenge	8/204	5/206	1/205
Rechallenge	5/8	3/5	0/1
(% positive)	(2.5%)	(1.5%)	(0)
104-93-3			
Challenge (non-irradiated vs irradiated)	8/27 vs 7/27	6/27 vs 5/27	2/27 vs 2/27
Rechallenge (non-irradiated vs irradiated)	5/8 vs 5/8	3/6 vs 3/5	1/3 vs 1/3
(% positive)	(18.5%)	(11.1%)	(3.7%)
107-96			
Challenge	16/49	9/46	0/44
Rechallenge	12/16	7/9	0/0
(% positive)	(24.5%)	(15.2%)	(0)

*% positive is calculated by dividing the number of subjects with positive rechallenge reactions by the total who underwent challenge.

The following Conclusions can be drawn from the material reviewed:

1. The dermal safety studies should be done on the to-be-marketed formulation. As the product proposed for marketing is a "solution", and the studies reviewed used a "lotion", it is unclear whether they represent the same product, even if the compositions are the same. The solubility of the ingredients may affect safety and efficacy, and hence the applicability of the conclusions to be drawn from the studies to the marketing formulation.

2. The dermal safety studies were not conducted under GLP, and the study reports contain internal inconsistencies. The design of the studies appears to be acceptable to obtain the needed information on the potential for dermal toxicity, although the provocation use test (PUT) in these studies is both inadequate and unnecessary. The Applicant has not presented their rationale in conducting photoirritation and photosensitization studies, which could be waived if none of the components of the drug product absorb in the UV-B, UV-A or the visible spectrum. However, it is known that diclofenac does absorb in the UV-B spectrum.

3. Dermal safety studies are usually performed on normal skin at the back or upper extremities in healthy volunteers. Caution should be exercised in the extrapolation of their data to other anatomic regions in specific patient groups. For instance, there was a much higher positive reaction rate in the sensitization testing in the phase 3 trial, 107-96, than in the contact sensitization study, 101-89-2. It is unclear whether differences in the population (older patients and overwhelming Caucasians in 107-96), previous therapies or the disease itself could be factors contributing to these variations.

4. It should be emphasized that contact sensitization testing involves a type IV dermal reaction for delayed hypersensitivity. Immune mechanisms such as anaphylaxis or other antibody-mediated reactions would not be tested by the studies submitted.

5. The data from the four dermal safety studies in this application suggest that PENNSAID Lotion is of low photoirritation and photosensitization potential. However, DMSO is by itself a known irritant, and the data suggest that the presence of diclofenac enhanced irritancy of the product. Interpretation of the sensitization testing data is complicated by the irritancy effect of DMSO and diclofenac (positive rates of 2.5%-18.5% for PENNSAID and 1.5%-11.1% for vehicle). In the phase 3 study, 107-96, the rates were even higher (24.5% for PENNSAID and 15.2% for vehicle). As a preparation containing diclofenac but not DMSO has not been tested, it is not possible to distinguish between irritation and sensitization from these studies. Because of this, the sensitization potential of PENNSAID is not excluded, but not proven.

6. One serious adverse event was reported in the four dermal safety studies (death due to cancer in 101-89-2). Other than skin test reactions, no other adverse events have been noted. Adverse event reporting in these studies appears to be inadequate. In the phase 3 trial, Study 107-96, the adverse events leading to discontinuation that might be related to the use of PENNSAID were rash, pruritus, halitosis and body odor, while desquamation ("dry skin") was observed in more than a third of patients. These risks should be carefully weighed against the benefits.

7. Systemic safety depends on systemic bioavailability, and would be supported by PK data, adverse event reporting, and clinical laboratory testing. The reviewed material does not contain PK information. In the phase 3 trial, Study 107-96, adverse event reporting and lab tests suggest that PENNSAID Lotion was well tolerated in general. Although transaminase elevation was observed in a patient using PENNSAID Lotion, its relationship to treatment is uncertain. Systemic exposure data would be helpful to determine whether the toxicities of oral diclofenac preparations, including liver toxicity, should be seriously considered for PENNSAID Lotion or not.