CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-947

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 4, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	20-947
Applicant Name	Nuvo Research, Inc.
Date of Submission	February 4, 2009, major amendment, July 31, 2009
PDUFA Goal Date	August 4, 2009 November 4, 2009 with clock extension
Proprietary Name / Established (USAN) Name	Pennsaid Topical Solution Diclofenac sodium topical solution
Dosage Forms / Strength	Topical solution 1.5% w/w (16 mg/mL)
Proposed Indication(s)	For the treatment of the signs and symptoms of osteoarthritis of the knee(s)
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Nick Olmos-Lau, M.D.; Jin Chen, M.D.
Statistical Review (for toxicology only)	Steven Thomson; Stella G. Machado, Ph.D.
Pharmacology Toxicology Review	Steven Leshin, D.V.M, Ph.D., Adam Wasserman, Ph.D., Paul Brown, Ph.D.
CMC Review	Olen M. Stephens, Ph.D.; Ali Al-Hakim, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	David Lee, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Mathilda Fienkeng, Twyla Thompson
DSI	N/A
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	N/A
OSE/DDRE	N/A
OSE/DRISK	Robin Duer, MBA, BSN, RN; Claudia Karwoski, PharmD
Other	N/A

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Pennsaid is a topical formulation of dicolfenac. The active ingredient is dissolved in dimethyl sulfoxide (DMSO), with the DMSO at 45.5% of the final formulation. The proposed indication for this product is for the treatment of the signs and symptoms of osteoarthritis of the knee(s). This is a 505(b)(2) application in which the sponsor is referencing NDA 19-201 for Voltaren tablets for certain carcinogenicity and reproductive toxicity data. Nuvo Research, Inc. also references Solaraze Gel for certain dermal and photo carcinogenicity data, but they have right of reference to that product's NDA.

2. Background

The application has a complex and lengthy regulatory history beginning with the original NDA submission to the former Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products (DAAODP) in December of 1997. Due to the complexity of this regulatory history and in order to provide clarity to the reader, I have attached the previous action letters and my previous summary review as appendices to this review. On October 26, 1998, the application was withdrawn due to manufacturing issues. DAAODP issued an advice letter [Appendix 1] on December 16, 1998 citing an absence of evidence for efficacy and fourteen CMC deficiencies. The application was resubmitted in August of 2001. An NA letter [Appendix 2] was issued on August 7, 2002, citing inadequate data to support efficacy, inadequate data to define the analgesic potential of the DMSO component and the safety of the high level of DMSO, and inadequate adverse event reporting and safety data from long-term studies. The sponsor submitted a response to the NA letter in June of 2006. In early 2005 DAAODP merged with the former Division of Anesthetic, Critical Care and Addiction Drug Products to form the current Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), so this "second cycle" resubmission was reviewed by the newly formed division. On December 28, 2006, DAARP issued an Approvable (AE) letter [Appendix 3]. While the sponsor had submitted adequate evidence of the efficacy and safety of their product for the proposed indication from new clinical studies, the division requested additional data to support the safety of the product specifically related to the high levels of DMSO, as well as four additional safety concerns due to a potentially genotoxic degradation impurity, extractables from the HDPE bottles in which the product was packaged, the potential for dermal carcinogenicity related to high DMSO exposure and the absence of photostability/photodegradation data. My review of the 2006 submission is attached as Appendix 4.

The specific approvability items listed in the 2006 AE letter were:

1. De monstrate that the DMSO component of the product does not, through its solubilizing properties, result in excessive exposure to likely environmental toxins and microbiological agents (e.g., DEET, sunscreen active components), and/or provide data to define a time period after product application during which patients must avoid these exposures and that can be appropriately addressed in the product labeling.
2. Asse ss the toxicological potential of PENNSAID® in repeat-dose dermal toxicology studies because of the potentially high level of absorption of the product components due to the DMSO and because DMSO is considered a novel topical excipient due to its high concentration.
3. L imit the ———— impurity, which contains a structural alert, to NMT ———— total daily intake. Therefore, tighten the acceptance criterion for this ———— in the drug product or characterize its genotoxic potential in a minimal genetic toxicology screen. b(4)

4. Limit the extractables from the HDPE bottles according to Agency guidelines or provide appropriate toxicological qualification of these impurities.
5. Switch all packaging from ———— to HDPE bottles, after addressing the toxicological potential of the extractables from the HDPE bottles as noted above. b(4)
6. Characterize the carcinogenic potential of PENNSAID® via dermal carcinogenicity studies, or provide an adequate scientific rationale for why such information is not necessary for the safe use of the product.
7. Conduct appropriate photostability studies to assess the potential for photodegradation impurities, and characterize the toxicity of any impurities found in these studies if above the qualification threshold described by ICH Q3b guidelines.

The sponsor submitted their response to the AE letter on February 4, 2009. During their review of the repeat-dose dermal toxicology studies, Drs. Leshin and Wasserman found that malignant multicentric lymphomas had developed in one low-dose female and one mid-dose female in a 26-week rat study. The sponsor was informed of the review team's concern regarding this finding and subsequently submitted additional data and a rationale for why they believed these events were not relevant. As this submission was received within three months of the PDUFA data, and as it was considered a major amendment, the review clock was extended for three months.

The CMC review team determined that the sponsor had provided adequate data in their resubmission to address the deficiencies outlined in the AE letter. Drs. Leshin, Wasserman and Brown initially agreed that the sponsor would need to further evaluate the lymphoma signal via completion of their ongoing dermal carcinogenicity study prior to the product being approved. Their conclusion was shared with the sponsor. The pharmacology/toxicology review team did find that the sponsor had adequately addressed their other concerns listed in the AE letter. However, during the course of his review, Drs. Stephens and Leshin raised additional concerns regarding the potential for extractability of toxic components from the bottle label due to rare instances of leakage of drug product with resultant smudging of the label ink. This concern has been adequately addressed on this review cycle as discussed below in Section 3.

In response to the toxicology review team's conclusions regarding the lymphomas noted in the rat study, the sponsor provided additional data and an evaluation by a group of expert toxicologic and veterinary pathologists. After reviewing this submission, Dr. Leshin remains convinced that the lymphomas represent a true signal of potential carcinogenicity, particularly due to the additional finding of two animals with epithelial thymomas in the 28-day rat study. However, Drs. Wasserman and Brown have concluded that the sponsor has provided an adequate and scientifically sound evaluation that supports their conclusion that these events did not represent a true signal for DMSO-induced cancers.

3. CMC/Device

Drs. Stephens and Al-Hakim initially concluded that the sponsor had submitted adequate data to address the CMC-related approvability items delineated in the 2006 AE letter. All product will be packaged in HDPE bottles. All extractables and leachables from the HDPE bottles were found to have been either adequately qualified based on the literature submitted or they were documented to be at sufficiently low levels so as to not provide a clinical concern. However, during the course of their review, the CMC review team raised concerns regarding the potential for extraction of components of the bottle label considering that rare instances of leakage with smudging of the label ink had been noted during storage. However, after further review, based on the small amount of damage to the label over a prolonged period of storage, the CMC reviewers concluded that this was not a significant problem in the clinical setting. Dr. Leshin continued to be concerned that patients would handle the bottles after applying the product and, thus, the potential remained for the extraction of toxic components from the label. This concern has been fully addressed at this time, however, as the sponsor has submitted an amendment in which they commit to incorporating an ——— ——————— on the bottles. b(4)

I concur with the review team that there are no outstanding CMC issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

Drs. Leshin, Wasserman and Brown have concluded that the sponsor has addressed most of the concerns raised in the AE letter. They have demonstrated that the high level of DMSO does not result in excessive exposure to environmental toxins when representative compounds were applied to the dried application site. As noted in Section 3, the sponsor has addressed the concerns regarding extractables and leachables from the product container. They have demonstrated that the photodegradants resulting from exposure of Pennsaid to prolonged light are similar to those found in another approved topical diclofenac product; and they have provided an adequate rationale to support addressing this issue via appropriate labeling. The review team has recommended that the sponsor complete their dermal carcinogenicity study and perform Fertility and Early Embryonic Development (Segment I) and Pre- and Postnatal Development (Segment III) reproductive toxicology studies as post-marketing requirements.

However, the review team has not reached agreement about the sponsor's evaluation and conclusions regarding the tumors noted in the rat toxicology study. Dr. Leshin remains convinced that the lymphomas and epithelial thymomas seen in the rat toxicology studies are a signal of potential carcinogenicity of the DMSO

that can only be considered adequately addressed by completion of the dermal carcinogenicity study. He, therefore, recommends that this study be completed prior to approval. However, Drs. Wasserman and Brown found the sponsor's evaluation to be compelling and have now concluded that there is not a signal for carcinogenicity, as per the following summary reproduced from page 4 and 5 of Dr. Wasserman's October 5th addendum to his supervisory review:

> I agree with Dr. Leshin that it will be of questionable usefulness to document the genetic relationship between the animals with lymphoma – which has not been provided at this time in any event – and it is difficult to confidently extrapolate carcinogenic potential from a 26-week treatment period (which is why this information does not suffice for a carcinogenicity evaluation in the first place). The lack of dose-response could look quite different at the end of 12- or 24-months of treatment. However, the narrow issue involved is whether or not the lymphomas, and now epithelial thymomas, represent a "signal" of potential carcinogenicity. The Applicant has assembled an impressive panel of experts in carcinogenesis on their own initiative, several of whom the Agency would likely have chosen to be independent experts on an Advisory Committee on this subject. The tissues from the study were read blind – unlike the original evaluation – and the panel was in complete agreement as to the findings and, combined with a number of additional arguments well described by Dr. Leshin, unanimously concluded these represented incidental and spontaneous findings and collectively was not a signal. The confirmation by another independent expert of the overall findings adds weight to what I believe already was an excellent and thorough evaluation of the study results by the Pathology Working Group. Therefore, upon consideration of these additional analyses and evaluations combined with arguments made previously by the Applicant – principally the lack of dose-response and absence of proliferative or pre-neoplastic findings, I do not agree with Dr. Leshin that the single incidence of lymphoma in a low- and mid-dose female and epithelial thymoma in 2 low-dose males represents a "signal" for potential carcinogenicity of DMSO in the 26-week toxicology study.
>
> Carcinogenicity studies are normally required prior to approval; however, the prior agreement reached with the Applicant was that the ongoing dermal carcinogenicity study could be completed post-approval in the absence of a signal from chronic toxicology studies. Based on the present understanding of the data, the carcinogenicity study will not be required pre-approval.

I concur with Drs. Wasserman and Brown that the sponsor has provided a compelling and scientifically sound evaluation to support their conclusion that the four events in the 26-week rat study do not represent a signal of carcinogenicity and that the sponsor may complete their ongoing dermal carcinogenicity study of DMSO post-marketing.

5. Clinical Pharmacology/Biopharmaceutics

While there were no specific concerns related to the clinical pharmacology or biopharmaceutics of Pennsaid listed in the AE letter, the sponsor submitted the results of two studies with this resubmission. The first was a relative bioavailability study comparing Pennsaid to Solaraze Gel. The results of that study documented that the diclofenac relative bioavailability from Pennsaid was approximately one-third of Solaraze under the maximum use conditions stated in

the products' labeling. The second study was conducted to determine the naturally occurring plasma levels of DMSO and $DMSO_2$ in healthy subjects on a regular diet who were not exposed to topical DMSO. DMSO levels were below the limit of quantitation and $DMSO_2$ levels were quantifiable in one-fifth of the subjects. Overall, the results of this study indicated that there is chronic exposure to low systemic levels of DMSO and $DSMO_2$ in healthy volunteers on a regular diet.

Drs. Lee and Doddapaneni have concluded that the information provided in this submission is acceptable and that no additional clinical pharmacology or biopharmaceutics data are necessary to support approval of the application. I concur with their conclusion.

6. Clinical Microbiology

No clinical microbiology data were necessary for submission and review of this application.

7. Clinical/Statistical-Efficacy

The reader is referred to my review of the previous submission [Appendix 4] which addresses the sponsor's adequate and well-controlled studies documenting the efficacy of Pennsaid for the treatment of osteoarthritis of the knee.

8. Safety

The reader is referred to my review of the previous submission [Appendix 4] which addresses the clinical safety of Pennsaid. Drs. Olmos-Lau reviewed the safety data from two new Phase 1 studies included in this submission. The first was a drying time study with 12 healthy subjects and the second was a trans-epidermal water loss study with 15 healthy subjects. No serious or unexpected adverse events were noted in either of these studies.

9. Advisory Committee Meeting

As Pennsaid does not contain a new molecular entity and is not a first in class product, and as there were no serious or unexpected safety signals and the sponsor provided adequate evidence of efficacy and product quality, discussion of the application at an advisory committee meeting was deemed to be unnecessary.

10. Pediatrics

Osteoarthritis is one of the indications for which studies required under the Pediatric Research Equity Act are waived due to its extremely infrequent occurrence in the pediatric population.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

There are no outstanding labeling issues at this time. Appropriate changes have been made by the review team and were agreed upon by the sponsor to address the concerns discussed elsewhere in this review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The sponsor has provided substantial evidence of the safety, efficacy and product quality in their application for Pennsaid. While the treatment effect appears modest, the safety profile is benign and therefore there is a reasonable risk-benefit profile. The sponsor will still need to provide further data from post-marketing studies to fully assess dermal carcinogenicity and reproductive toxicity. However, the data available at this time do not raise concerns that would preclude approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  As diclofenac is an NSAID, Pennsaid will require an NSAID Medication Guide and, therefore, a Medication Guide-only REMS.

- Recommendation for other Post-marketing Requirements

As explained in Section 4 above, the following post-marketing requirements will be included in the approval letter:

  - An evaluation of the potential carcinogenicity of DMSO in a 2-year bioassay in the rat

- An evaluation of Fertility and Early Embryonic Development in a single species with DMSO

- An evaluation of Peri-and Postnatal Development in a single species with DMSO

APPENDIX 1

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 16 1998

NDA 20-947

Dimethaid Research Inc
Attention: Zev Shaimhouse, MD, BSc., FRCPC
Medical Director
1405 Denison Street
Markham, Ontario L3R 5V2

Dear Dr. Shaimhouse:

As we agreed, here is a list of the medical and chemistry deficiencies to date for your new drug application (NDA) dated December 15, 1997, received January 8, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pennsaid (diclofenac sodium lotion) 1.5% and withdrawn on October 27, 1998. Please be advised that the NDA review was not completed, and the list could be amended with the discovery of new deficiencies after the NDA is resubmitted.

LIST OF DEFICIENCIES AND COMMENTS

MEDICAL
Study 102-93-1 does not provide substantial evidence of efficacy of Pennsaid, because the primary variable did not show a statistically significant difference between Pennsaid and control.

CHEMISTRY

Recently, our inspectors could not complete inspection of your manufacturing facilities for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. A satisfactory inspection will be required before this application may be approved.

Major deficiencies:

1. Please explain the excessively wide point-to-point variability of your stability data, especially the dimethyl sulfoxide (DMSO) assay, diclofenac sodium assay and diclofenac sodium impurity assay data. Do these data accurately reflect the behavior of the product over time? Do they indicate a problem with the analytical methodology?

2. There are no primary stability data for Pennsaid packaged in the 15 and ——— sizes, i.e., packaged in the container/closure systems described in this NDA. The stability reports submitted for these sizes indicate that they were packaged in ——— bottles. This does not match the container information provided in the NDA. b(4)

3. All stability reports must include the initial point data. Only one of the submitted 25°C reports contains these data.

4. The proposed "shelf life" impurity specifications for Pennsaid are set too high. Please submit impurity specifications which are justified by the stability data.

5. Please provide data showing that the proposed ——— container/closure system is chemically and physically compatible with the drug product. b(4)

6. Please provide data on the photostability of Pennsaid. This was requested at the pre-NDA meeting.

7. Please provide data for the Preparatory Testing section of the USP Microbial Limits chapter to show that the testing is valid for this product. This was requested at the pre-NDA meeting.

Other deficiencies:

8. A maximum mixing time should be established and validated for the dissolution of the diclofenac sodium ———. This was requested at the pre-NDA meeting. b(4)

9. A maximum hold time between the manufacture of the product (through ——— and filling into the bottles should be established and validated. This was requested at the pre-NDA meeting.

10. Please clarify whether the "Regulatory Specifications and Methods Used to Test Pennsaid After June 1, 1997" will be used as regulatory specifications for the post-approval testing of the product marketed in the US.

11. Please state the expected shelf life for each fill size.

12. Please clearly indicate the stability protocol which will be used for the post approval and annual batch studies.

13. The container labels should be revised as follows:
    a. The ethanol content must be stated (as w/w).
    b. The ——— statement should be replaced with "℞ (or Rx) only". b(4)
    c. The term ——— should be replaced with "Other".
    d. The storage statement should be revised to read "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."

14. The package insert should be revised as follows:
    a. In the Description section, only one version of the chemical name is needed.
    b. In the Description section, providing the amounts of each inactive component is optional.
    c. In the How Supplied section, a brief description of the container should be provided, i.e., in ——— with dropper caps. b(4)
    d. The storage statement should be revised to read "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."
    e. The ——— statement should be replaced with "℞ (or Rx) only."

If you have any questions, contact Victoria Lutwak, Project Manager, at (301) 827-2090.

Sincerely,

JEH 12-16-98

John Hyde, Ph.D., MD
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 20-947
HFD-550/Div. Files
HFD-550/Averbuch/Patel/Yaciw/Wang/Weir
HFD-550/CSO/Lutwak
HFD-725/Lin/Taneja

Drafted by: VL/November 1, 1998

final;
filename: 981101DE.WPD
Deficiencies

APPENDIX 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-947

Dimethaid Research, Inc.
Attention: Dr. Frederick N. Ballantyne
10455 North Central Expressway
Suite 109 PMB 320
Dallas, Texas 75231-2213

Dear Dr. Ballantyne:

Please refer to your new drug application (NDA) dated August 7, 2001, received August 8, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pennsaid (diclofenac sodium) Topical Solution 1.5% w/w.

We acknowledge receipt of your submissions dated September 20, and October 5, 2001, February 13, March 28, April 3, May 7, May 8, and June 28, 2002.

You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review and find the information presented is insufficient to determine if the drug is safe and effective under the proposed conditions of use. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Clinical Deficiencies:

Efficacy:

There is insufficient information to conclude that Pennsaid applied topically to a knee is efficacious for that particular knee. Demonstration of efficacy at the site of application is critical for approval of a topical formulation.

In both pivotal Studies 109 and 109-US, the compassionate use of therapy was extremely high. This confounds analysis of the data. Therefore, in an attempt to understand the data as well as possible, the Division reanalyzed the data with patients being assigned into one of three treatment categories. Category 1 patients had the target knee-only treated during the entire study. Category 2 patients had the target and non-target knee treated during the entire study. Category 3 patients had the target knee treated during the entire study, but also may have treated their non-

target knee during some portion of the study. Of the number of Intent to Treat (ITT) patients for Study 109 and 109-US combined (536 patients), the following number of patients were included in Categories 1, 2, and 3, respectively: 111 (21% of total), 348 (65% of total), and 77 (14% of total).

Such a large extent of contralateral use confounds the analysis of efficacy of a topical therapy. There was no prespecified stratification of patients into these three treatment arms; patients were allowed to apply treatment to more than one knee based on a "compassionate" basis. Therefore, the effects of randomization in any subanalysis based on category were lost.

Only in Category 2 (both knees treated during the entire study) was there a statistical support for efficacy for the three co-primary endpoints. In Category 2, the trends were inconsistent.

Efficacy must be demonstrated in the three co-primary endpoints of pain (WOMAC pain subscale), function (WOMAC function subscale) and patient global. The results for Pennsaid do not demonstrate efficacy in the Category 1 and 3 patients. In the Category 2 patients, only a single knee was analyzed for efficacy and so it is unknown if there was clinical benefit in the other treated knee.

The reanalysis of data, as described in the clinical efficacy section above, formed the basis for the statistical review of this NDA. This was because the primary analysis presented in the NDA excluded many randomized patients in Study 109 and 109-US. All randomized and treated patients are typically included in an ITT analyses. Several such analyses with different imputation methods for missing values were performed by the Division. These analyses show that, depending on the imputation method, the results of the NDA's primary analysis are reversible.

From a trial design point of view, there were no scheduled measurements made between baseline and final assessments from 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 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 these issues.

Safety:

Inadequate data was provided to demonstrate long-term safety for this drug product.

In addition, demonstration of safety in situations of co-administered therapies, which is likely to occur once a topical agent is approved, is needed. No safety information on the use of Pennsaid with daily oral anti-inflammatory and analgesic therapies was provided.

There are no clinical laboratory data and no data on co-administration with other drugs (except rescue acetaminophen) in either Study 109 or 109-US.

There are substantial differences in reporting of some adverse events (AEs) between Studies 109 and 109-US and other NDA studies. For example, arthralgia is listed to occur between 1.9-3.7% for the Pennsaid groups in Study 109 and 109-US, but 34.5% in Study 107-96.

Similarly, arthralgia was noted in 1.9-4.6% of patients treated with DMSO in Study 109 and 109-US, but in 40% of DMSO treated patients in Study 107-96. It is unclear why this difference exists. Since DMSO is an important component of Pennsaid, all AEs in these two groups in Study 109 and 109-US are considered to occur with Pennsaid. Therefore, there is no clear understanding of the adverse event profile of Pennsaid versus a "non-diclofenac" 45.5% DMSO-containing control.

Under ICH guidelines the Sponsor is required to submit safety data from the sample size of 300-600 patients treated for 6 months and from 100 patients treated for 12 months. You have submitted data from two open-label, long-term studies, EDR and 105-95.

There are no AEs reported for EDR. The rates of AEs in Study 105-95 are very low compared to controlled studies even for skin reactions that are very common with the use of this drug. This is suggestive of very significant underreporting and, therefore, cannot be viewed as adequate safety data for long-term use of the drug.

Because of the above deficiencies, the safety of Pennsaid has not been adequately demonstrated in this NDA.

Clinical Pharmacology/Biopharmaceutics Deficiencies:

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 order to address the issue of local (sub-stratum corneum) depot formation, you are encouraged to evaluate the uptake of DMSO and diclofenac into the different layers of skin using microdialysis.

Additional requests:

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Review of the literature and labels for DMSO, along with efficacy results for Study 102-93-1 and adverse events (i.e. paresthesia at site) in Study 107-96 suggest DMSO is an active component of Pennsaid. Therefore, Pennsaid may represent a combination product which will need to be studied as such in future trials.

2. Describe in detail any significant changes or findings in the safety profile.

3. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   Present tabulations of the new safety data combined with the original NDA data.

   Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

   For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

4. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

5. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

6. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, M.D.
Director
Division of Anti-Inflammatory, analgesic,
and Ophthalmic Drug Products
Office of Drug Evaluation ODE V
Center for Drug Evaluation and Research

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

/s/

Lee Simon
8/7/02 09:36:56 AM

APPENDIX 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-947

Dimethaid International, Inc.
2220 Chalkwell Dr.
Midlothian, VA 23113-3884

Attention: Frederick Ballantyne, M.D.
Director, Clinical Research and Regulatory Affairs

Dear Dr. Ballantyne:

Please refer to your December 15, 1997, new drug application (NDA) which was withdrawn October 26, 1998, and resubmitted August 7, 2001, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (diclofenac sodium topical solution) 1.5% w/w.

We acknowledge receipt of your submissions dated January 8 and 14, March 26 and 31, April 7 and 29, July 31, and October 26, 1998, August 7, September 20, October 5, and December 3, 2001, February 13, March 28, April 3, May 7 and 8, June 28, July 26, September 24, and November 7, 2002, October 6, 2003, and June 28, August 17, September 18 and 29, October 11, 12, 13, 23, 25, 26, and 27, and November 8, 10, and 15, 2006.

Your submission dated June 28, 2006, constituted a complete response to our August 7, 2002, action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

1. Demonstrate that the DMSO component of the product does not, through its solubilizing properties, result in excessive exposure to likely environmental toxins and microbiological agents (e.g., DEET, sunscreen active components), and/or provide data to define a time period after product application during which patients must avoid these exposures and that can be appropriately addressed in the product labeling.

2. Assess the toxicological potential of PENNSAID® in repeat-dose dermal toxicology studies because of the potentially high level of absorption of the product components due to the DMSO and because DMSO is considered a novel topical excipient due to its high concentration.

3. Limit the ———— impurity, which contains a structural alert, to NMT —— micrograms total daily intake. Therefore, tighten the acceptance criterion for this —— impurity to NMT —— in the drug product or characterize its genotoxic potential in a minimal genetic toxicology screen. b(4)

4. Limit the extractables from the HDPE bottles according to Agency guidelines or provide appropriate toxicological qualification of these impurities. b(4)

5. Switch all packaging from ———— to HDPE bottles, after addressing the toxicological potential of the extractables from the HDPE bottles as noted above.

6. Characterize the carcinogenic potential of PENNSAID® via dermal carcinogenicity studies, or provide an adequate scientific rationale for why such information is not necessary for the safe use of the product.

7. Conduct appropriate photostability studies to assess the potential for photodegradation impurities, and characterize the toxicity of any impurities found in these studies if above the qualification threshold described by ICH Q3b guidelines.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. Include an integrated safety dataset from all Phase 3 clinical trials. The variable names in the datasets should be kept consistent across trials.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   b. Present tabulations of the new safety data combined with the original NDA data.

   c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
12/28/2006 04:32:49 PM

APPENDIX 4

DIVISION DIRECTOR SUMMARY REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	December 28, 2006
DRUG:	PENNSAID® Topical Solution (diclofenac sodium topical solution) 1.5% w/w
NDA:	20-947
NDA Code:	Type 3S NDA
SPONSOR:	Dimethaid International, Inc.
INDICATION:	For use as a topical treatment for relief of the signs and symptoms of osteoarthritis of the knee(s)

Dimethaid International, Inc. submitted NDA 20-947 in support of marketing approval for PENNSAID® Topical Solution (diclofenac sodium topical solution) 1.5% w/w on December 15, 1997. The sponsor withdrew the application on October 27, 1998, but a "deficiencies" letter was, nevertheless, issued on December 16, 1998. It cited fourteen CMC deficiencies and noted that one of the pivotal efficacy trials (Study 102-93-1) failed to demonstrate statistical significance and did not provide substantial evidence of efficacy. A response to the letter was submitted on August 7, 2001 and a not-approvable letter was issued on August 7, 2002. That letter cited several deficiencies regarding the evaluation of safety and efficacy. After meetings with the former Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, the sponsor redesigned their clinical development plan and then conducted two additional clinical studies and additional pharmacokinetic studies.

Review of the CMC portion of this response was completed by Sue-Chin Lin, Ph.D. Ravi Harapanhalli, Ph.D. provided a supervisory memo regarding the CMC deficiencies noted in the resubmission. Review of the pharmacology and toxicology data presented in the submission was completed by L. Steven Leshin, D.V.M., Ph.D. A supervisory pharmacology/toxicology review was provided by Daniel Mellon, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the submission was completed by David Lee, Ph.D. The clinical review was completed by Larissa Lapteva, M.D. and a statistical review was completed by Thomas Permutt, Ph.D. Jeffrey Siegel, M.D. provided a supervisory clinical review. Consultations on this response were also obtained from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Office of Surveillance and Epidemiology (OSE).

The deficiencies listed in the August 7, 2002, not-approvable letter were:

1. The re was insufficient data to support the efficacy of the product. This was based on the review team's concern that, due to frequent use of the study drug on the non-target knee (for compassionate purposes), the target-knee data were confounded in both pivotal clinical trials (Studies RA-CP-109 and RA-CP-109US). In addition, the sponsor's analyses of the data were not based on the ITT population, and the Division's reanalyses based on the correct population did not confirm efficacy. The letter also cites an absence of scheduled measurements between baseline and final assessments for either of the efficacy studies.

2. I nadequate data were provided to support the long-term safety of the product and to assess drug-drug interactions, particularly with oral NSAID or analgesic therapy.

3. The re was inadequate collection of laboratory data during the clinical studies.

4. The pharmacokinetic data submitted did not adequately evaluate the DMSO component of the formulation.

An additional request that was included in the letter, but not clearly designated as a deficiency, was that the sponsor study PENNSAID® as a combination drug product in future trials, due to suggestions from the literature that the DMSO component is active as an analgesic/anti-inflammatory agent.

The sponsor has responded to the first deficiency by submitting the results of a new clinical trial and by reanalyzing the results of Study RA-CP-109US, which had been submitted with their previous response. The new study, Study PEN-03-112, was a 12-week, adequate and well-controlled study that compared PENNSAID® to placebo and vehicle. Drs. Lapteva, Permutt and Siegel have thoroughly reviewed the results of these studies and the reader is referred to their excellent reviews for further detail. Both studies demonstrated a statistically significant treatment effect for PENNSAID® on the co-primary endpoints, WOMAC pain, physical function and patient global assessment. Sensitivity analyses using a variety of imputation methodologies for missing data

supported these results for Study RA-CP-109US. In addressing the additional request, the data from Study PEN-03-112 provide evidence that DMSO is not in and of itself an active drug component of the product.

The inadequate characterization of safety and of drug-drug interactions, and the inadequate collection of laboratory data noted in the second and third deficiencies were appropriately addressed by the sponsor with the collection of additional data in their 12-month, open-label extension study (PEN-03-112E). Drs. Lapteva and Siegel have reviewed this data and found that the only adverse event of significant clinical concern that does not already fall under the labeled safety profile of diclofenac is "application site reaction." These reactions occurred frequently and sometimes resulted in discontinuation from the study, but were generally mild to moderate and resolved once treatment was discontinued. Of note, Study PEN-03-112 included a combination oral diclofenac and PENNSAID® arm which demonstrated a clear increase, compared to treatment with either product alone, in the adverse events known to occur with NSAID exposure.

Dr. Lee has determined that the final deficiency was also adequately addressed in this resubmission with additional single-dose and multiple-dose pharmacokinetic data on diclofenac, DMSO and $DMSO_2$, the major metabolite of DMSO.

As a result of the reviews of the CMC and pre-clinical data that have been submitted to this NDA, the CMC and pharmacology/toxicology review teams have determined that additional deficiencies exist that must be addressed before the application may be approved.

Nonclinical Safety:

Drs. Leshin and Mellon have identified six deficiencies which must be addressed prior to the approval of PENNSAID®.

1. The sponsor has failed to adequately assess the potential for the DMSO component of PENNSAID® to increase the absorption of potentially toxic substances and/or infectious agents that may come into contact with the site after application of the drug product, e.g. DEET, sunscreen components, household chemicals, residual dry-cleaning chemicals, viral and bacterial agents.

2. The sponsor has not adequately characterized the toxicological potential of the DMSO component of PENNSAID®. As DMSO has not previously been approved for chronic topical use on intact skin and is, therefore, considered a novel excipient, it must be characterized in repeat-dose toxicology studies. In particular, the potential toxicity due to the combined absorption of DMSO, diclofenac, glycerin, propylene glycol and ethanol must be addressed with appropriate data.

3.As pe r the CMC deficiency noted below, the sponsor must submit data that establishes that exposure to extractables from the plastic packaging will be no greater than that expected to result from the use of similar packaging components when used with foods, or that the exposure is considered acceptable based on supportive toxicological data.

4.As pe r the CMC deficiency noted below, the sponsor must tighten the ——— impurity, which contains a structural alert, to NMT —— micrograms total daily intake or provide adequate safety data to qualify the impurity through conduct of a minimal genetic toxicity screen. b(4)

5.The sponsor has not provided adequate characterization of the carcinogenic potential of PENNSAID® and must, therefore, conduct dermal carcinogenicity studies with the product, or provide an adequate scientific rationale for why such information is not necessary for the safe use of the product.

6.The sponsor has not provided adequate data to assess the photostability of PENNSAID® in order to characterize the potential toxicity associated with photodegradation products that may exist. Therefore, they must conduct appropriate photodegradation studies.

Chemistry, Manufacturing and Controls:

Drs. Lin and Harapanhalli have identified three deficiencies which must be addressed prior to approval of PENNSAID®.

1.PENNSAI D® contains a —— impurity which is an ——————— product of diclofenac sodium and a ———————————. This degradation product is a structural alert for genotoxicity and must be controlled at a level not to exceed a total daily intake of—— micrograms. Therefore, the acceptance criterion for this —— impurity must be tightened to NMT ——— in the drug product, or adequate safety data to qualify the impurity must be provided in a minimal genetic toxicity screen. b(4)

2.The results of USP tests on the —— HDPE bottle indicate that the PENNSAID® vehicle extracts a maximum quantity of plastic material from HDPE compared to other vehicles that are considered representative of a potential interaction of foods with plastics. As the Agency guidance on container closure systems for packaging human drugs and biologics recommends that, for liquid-based drug products with chronic dosing regimens that contain co-solvents, data should be provided to establish that exposure to the extractables will be no greater than that expected to result from the use of similar packaging components when used with foods, or that the exposure is considered acceptable based on supporting toxicological data, the sponsor must provide data on the chemical nature of the materials extracted by the PENNSAID® vehicle and data supporting b(4)

their toxicological qualification. This is particularly important due to the fact that the formulation of this product contains 45.5% DMSO, a strongly extracting solvent and skin penetration enhancer that can potentially facilitate percutaneous absorption of otherwise non-absorbable chemicals.

3. The sponsor has proposed switching their current packaging plans from ——— to HDPE bottles for all product strengths. However, due to limited available stability data, they have proposed to switch only the ——— fill size to HDPE bottles pre-approval, and to switch to HDPE bottles for the ——— and 60-mL sizes post-approval. The stability data on the ——————— packaging units indicates that these bottles may not provide adequate protection as a significant loss of alcohol was observed from all bottle sizes. Therefore, the sponsor must switch all product sizes to HDPE bottles following acceptable safety qualification of the HDPE bottles. Additional bridging stability data will also be required. b(4)

Discussion:

The sponsor has provided data that demonstrates that PENNSAID® is effective when used according to the proposed labeling. Although there were no adverse events noted in the clinical studies that would preclude approval, based on a thorough review of the CMC and pre-clinical data that has been submitted to the application, the CMC and pharmacology/review teams have noted a number of deficiencies that bring into question the quality and safety of the product, and which must be appropriately addressed with additional data before PENNSAID® can be approved for marketing. While these deficiencies were not explicitly noted in the previous action letters, they were certainly implicitly contained in the requests for adequate safety data to support the approval.

In order to address these deficiencies, the sponsor will need to:

- Demonstrate that the DMSO component of the product does not, through its solubilizing properties, result in excessive exposure to likely environmental toxins and microbiological agents (e.g., DEET, sunscreen active components), and/or provide data to define a time period after product application during which patients must avoid these exposures and that can be appropriately addressed in the product labeling.

- Assess the toxicological potential of PENNSAID® in repeat-dose dermal toxicology studies because of the potentially high level of absorption of the product components due to the DMSO and because DMSO is considered a novel topical excipient due to its high concentration.

- Limit the ——————— impurity, which contains a structural alert, to NMT ——micrograms total daily intake. Therefore, tighten the acceptance criterion for this ——— impurity to NMT ——— in the drug product or characterize its genotoxic potential in a minimal genetic toxicology screen. b(4)

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Action:

Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
12/28/2006 04:14:18 PM
MEDICAL OFFICER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20947	ORIG-1	NUVO RESEARCH INC	PENNSAID(DICLOFENAC SODIUM)1.5% TOP LOTI

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/s/

JESSICA M BENJAMIN
11/04/2009

BOB A RAPPAPORT
11/04/2009

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR SUMMARY REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	December 28, 2006
DRUG:	PENNSAID® Topical Solution (diclofenac sodium topical solution) 1.5% w/w
NDA:	20-947
NDA Code:	Type 3S NDA
SPONSOR:	Dimethaid International, Inc.
INDICATION:	For use as a topical treatment for relief of the signs and symptoms of osteoarthritis of the knee(s)

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Action:

Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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MEDICAL OFFICER