

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-947

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 04/30/10
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

020-947

NAME OF APPLICANT / NDA HOLDER

Nuvo Research Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

PENNSAID® Topical Solution (diclofenac sodium topical solution) 1.5% w/w

ACTIVE INGREDIENT(S)

diclofenac sodium USP

STRENGTH(S)

1.5%w/w diclofenac sodium

DOSAGE FORM

Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
1/29/2009

Loucaides

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Tina Loucaides, Chief Counsel, Intellectual Property of Nuvo Research Inc.	
Address 10-7560 Airport Road	City/State Mississauga, Ontario CANADA
ZIP Code L4T 4H4	Telephone Number 1-866-652-9473
FAX Number (if available) 1-866-652-9476	E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED WITH THE
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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

020-947

NAME OF APPLICANT / NDA HOLDER

Dimethaid International Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

PENNSAID® Topical Solution (1.5% w/w diclofenac sodium)

ACTIVE INGREDIENT(S)

diclofenac sodium USP

STRENGTH(S)

1.5%w/w diclofenac sodium

DOSAGE FORM

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E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

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ZIP Code

FAX Number (if available)

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the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

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- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p><i>June 23, 2006</i></p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Mimi D. Brennan, Director, Regulatory Affairs & Clinical Research Nuvo Research Inc. (Regulatory Affairs for Dimethaid International Inc.)</p>	
<p>Address Los Abedules, Appleby Gardens</p>	<p>City/State St. James, Barbados</p>
<p>ZIP Code</p>	<p>Telephone Number 1-866-652-9473 Ext. 2293</p>
<p>FAX Number (if available) 1-866-652-9476</p>	<p>E-Mail Address (if available) mbrennan@nuvoresearch.com</p>



NUVO

February 4, 2009

PATENT CERTIFICATION

Nuvo Research Inc. makes the following certification with respect to the patents listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book") for the listed drug product diclofenac sodium, which is approved under NDA No. 21-005.

The following certification is made in accordance with FDC Act § 505(b)(2)(A) and 21 C.F.R. § 314.50(i) and is submitted to pending NDA No. 20-947.

Paragraph IV Certification

Nuvo Research Inc. certifies that, in the opinion of Nuvo Research Inc. and to the best of its knowledge, U.S. Patents No.

5,792,753,

5,852,002 (claims 2, 3, 4, 8, and 9),

5,914,322,

5,929,048 (claims 2, 3, and 4), and

5,985,850

are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of diclofenac sodium, for which this application is submitted.

Nuvo Research Inc. hereby states that the company is simultaneously sending the required notice to the holder of NDA No. 21-005, and to the owners of the above-referenced patents. This notice, which is being sent by certified mail, return receipt requested, meets the requirements of FDC Act § 505(b)(3)(D) and 21 C.F.R. § 314.52(c) regarding notice content.

Sincerely,

Tina Loucaides
Chief Counsel, Intellectual Property



NUVO

February 4, 2009

PATENT STATEMENT

Nuvo Research Inc. makes the following statement in accordance with FDC Act § 505(b)(2)(B) and 21 C.F.R. § 314.50(i)(1)(iii)(A).

U.S. Patents No.

5,639,738,

5,852,002 (claims 1, 5, 6, 7, 10, and 11), and

5,929,048 (claims 1, 5, 6, and 7)

are method-of-use patents listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") for diclofenac sodium (NDA No. 21-005) with a U-402 patent use code, which is described as: TREATMENT OF ACTINIC KERATOSES.

U.S. Patents No. 5,639,738, 5,852,002 (claims 1, 5, 6, 7, 10, and 11), and 5,929,048 (claims 1, 5, 6, and 7) do not claim any of the proposed indications in Nuvo Research Inc.'s 505(b)(2) application for diclofenac sodium.

Sincerely,

Tina Loucaides
Chief Counsel, Intellectual Property



DIMETHAID INTERNATIONAL INC.

Regulatory Affairs Department
10 - 7560 Airport Road
Mississauga, Ontario, CANADA, L4T 4H4
Tel.: (905) 673-6980 Fax: (905) 673-0127

NDA 020-947

New Drug Application

PENNSAID® Topical Solution
(1.5% w/w diclofenac sodium)

Patent Certification—No Relevant Patents
21 CFR 314.50 (i)(1)(ii)

Dimethaid International Inc., a fully-owned subsidiary of Nuvo Research Inc., hereby certifies that the patent status of the subject drug, Pennsaid Topical Solution (1.5% w/w diclofenac sodium), is as follows:

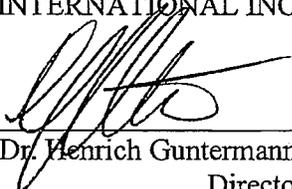
In the opinion and to the best knowledge of Dimethaid International Inc. there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

This certification is made in accordance with 21CFR314.50(i)(1)(ii).

Dated, this 23 day of June, 2006.

DIMETHAID INTERNATIONAL INC.

Per: _____

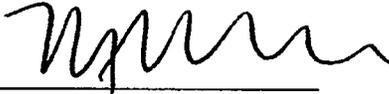

Dr. Henrich Guntermann,
Director

PATENT CERTIFICATION

The applicant, DIMETHAID RESEARCH INC., hereby certifies that in connection with the attached New Drug Submission for Pennsaid™, it has relied upon United States Patent Number 4,575,515 dated March 11, 1986 and United States Patent Number 4,652,557 dated March 24, 1987 and that it is the holder of both patents.

Dated, this 15th day of December, 1997.

DIMETHAID RESEARCH INC.

Per: 

Rebecca E. Keeler,
President and CEO.

Patent Information

The following US Patents cover the formulation, composition, and/or method of use of PENNSAID® Topical Solution. This product is the subject of this application for which approval is being sought.

US Patent Number	Expiration Date	Title	Type of Patent	Patent Owner
4,575,515	May 11, 2006	Pharmaceutical solutions comprising dimethyl sulfoxide	Drug Product	Dimethaid Research Inc.*
4,652,557	March 24, 2007	Pharmaceutical solutions comprising dimethyl sulfoxide	Drug Product	Dimethaid Research Inc.*

Attached are copies of the front and claim pages of US Patents Numbers 4,575,515 and 4,652,557.

*The applicant, Dimethaid International Inc., is a wholly-owned subsidiary of Dimethaid Research Inc.

United States Patent [19]
Sandborn

[11] Patent Number: 4,575,515
[45] Date of Patent: Mar. 11, 1986

- [54] PHARMACEUTICAL SOLUTIONS
COMPRISING DIMETHYL SULFOXIDE
- [75] Inventor: Edmund Sandborn, Burlington,
Canada
- [73] Assignee: Clark Pharmaceutical Laboratories
Ltd., Weston, Canada
- [21] Appl. No.: 610,590
- [22] Filed: May 15, 1984
- [51] Int. Cl.⁴ A61K 31/10
- [52] U.S. Cl. 514/708; 514/936;
514/647
- [58] Field of Search 514/708, 936
- [56] References Cited

U.S. PATENT DOCUMENTS

3,551,554 12/1970 Herschler 424/45

3,711,602 1/1973 Herschler 424/45
3,740,420 6/1973 Herschler et al. 424/45
3,743,727 7/1973 Herschler 514/936
4,353,896 10/1982 Levy 514/936
4,369,190 1/1983 Schulte 514/936

FOREIGN PATENT DOCUMENTS

1001075 12/1976 Canada .
1005761 2/1977 Canada .

Primary Examiner—Ronald W. Griffin
Attorney, Agent, or Firm—James D. Fornari; Ivor M.
Hughes

[57] ABSTRACT

Novel pharmaceutical solutions and particularly novel
pharmaceutical solutions comprising dimethyl sulfoxide
(DMSO).

48 Claims, No Drawings

PHARMACEUTICAL SOLUTIONS COMPRISING
DIMETHYL SULFOXIDE

FIELD OF INVENTION

This invention relates to novel pharmaceutical solutions and particularly novel pharmaceutical solutions comprising dimethyl sulfoxide (DMSO).

BACKGROUND OF THE INVENTION

If one rubs a few drops of DMSO on any part of his/her person, it is usually absorbed very rapidly and a taste resembling garlic is immediately present. This finding subsequently led to a most important finding of pharmacologic ability of pure DMSO of various strengths to reduce inflammation and pain in a wide range of conditions to penetrate into the skin after topical application of DMSO for the lessening of pain and swelling of inflammation. Many clinicians have reported particularly gratifying results by the use of DMSO in the management of arthritis.

U.S. Pat. No. 3,549,770 teaches the topical application of undiluted dimethyl sulfoxide, and dimethyl sulfoxide with appropriate pharmaceutical diluents, excipients and adjuvants in the treatment of tissue damage, pain, abnormal muscle contraction and vascular insufficiency.

The facility with which DMSO penetrates the skin and other membranes has spawned considerable research into the use of DMSO as a vehicle for the administration of drugs through topical application. In the course of that research a number of different products were added to DMSO with ranging degrees of success.

U.S. Pat. No. 3,711,606 teaches the use of DMSO as a carrier in concentrations of 50% and over by weight with a steroid in lotion, cream, gel and ointment forms to penetrate rapidly to and saturate the stratum corneum, the highly resistant "horny layer" of the skin which is the major barrier to penetration.

According to this patent "The Steroid continues to penetrate through the skin from this reservoir in the stratum corneum to the underlying tissue and into the circulatory system" (Column 3, Line 50-53).

U.S. Pat. No. 3,711,602 also teaches the compositions (creams, suppositories, ointments and gels) for topical application for enhancing tissue penetration of physiologically active agents (for example, physiologically active steroids, antineoplastic agents, antigens, antihistamine agents, neuropharmacologic agents, anti-inflammatory agents, anticoagulants, vasodilators, ultra-violet screening agents and agents with DMSO).

However, these compositions are extremely greasy and are solely for surface penetration, very little penetrating deeply into affected areas where the greatest need arises. See also U.S. Pat. Nos. 3,551,554; 3,740,420; 3,743,727; 3,790,682; 4,369,190 and 3,499,961 and Canadian Letters Patent Nos. 1,001,075; 1,011,255; 1,043,704; 980,252 and 1,005,761.

Furthermore these compositions are not suitable where there is a need for rapid deep penetration of medicine for direct application to an affected part of the body (joints etc.). In addition, DMSO also captures water from the skin, being a hydroxyl ion scavenger thereby dehydrating the skin.

It is therefore, an object of this invention to provide penetrating solutions, allowing penetration deeply into affected parts of the body, comprising DMSO, preferably another medicine, which may be applied topically

and which rapidly penetrates deeply into the body carrying the medication in the solutions with it while protecting the skin against dehydration.

Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of the embodiments thereof.

SUMMARY OF THE INVENTION

According to one aspect of the invention, a deeply and rapidly penetrating homogeneous solution for topical application causing medicine to penetrate deeply and rapidly into affected parts of the body without irritating the skin or leaving a greasy film on the skin when the solution is applied topically is provided, the solution comprising:

- (a) between about 40% and about 85% DMSO by weight of the solution, more preferably between about 60% and about 70% DMSO by weight of the solution of most preferably about 65% DMSO by weight of the solution;
- (b) a polyalcohol, preferably having 3-5 carbon atoms, for the retention of moisture in the skin, in one embodiment, glycerol or glycerine;
- (c) a dispersant for assisting to disperse the components in solution to provide a homogeneous solution when applied to the skin and when penetrating the skin, in one embodiment propylene glycol;
- (d) a medicine, for example Naproxen and Diclofenac dissolved in the solution;
- (e) water.

Because the medicine must be dissolved in the solution, a solubilizing agent may be added to the solution to dissolve the medicament. For example, Naproxen is not soluble in DMSO. Therefore, Ethanol is used to solubilize the Naproxen for addition to the solution. Xylocaine may also be added to the solution where desired.

When the penetrating solutions of the invention are employed in topical applications unexpected results from treatment therewith are obtained. This is because of the ability of the solution to penetrate quickly and deeply into the body through the skin and tissue below the point of topical application. Furthermore, because of the nature of the solution, the skin is not dried out. Where glycerol is employed, glycerol is a hydroxyl radical scavenger (as is DMSO) and assists in the medicinal effect of the DMSO in the solution. The dispersant propylene glycol is also a hydroxyl radical scavenger.

The formulations are prepared by combining the requisite amounts of the ingredients together (adding solubilizing agents, for example Ethanol where Naproxen is to be included). The medicines that may be used with the DMSO may be manufactured according to the processes taught in the following patents or other such suitable processes.

NAPROXEN:	Canadian Letters Patent: 1,122,603 1,004,226 1,142,957 1,137,108 879,118 879,719 936,171 955,600 960,668 960,689 983,517 991,655 1,000,725 1,000,726 1,020,575 1,124,735
DICLOFENAC:	Canadian Letters Patent: 850,133 811,738 829,910 918,175 765,432 827,708 1,126,746 1,050,365
NIFEDIPINE:	Canadian Letters Patent: 961,582 934,758 868,911 921,035 1,080,223

The invention will now be illustrated having regard to the following embodiments and exemplary test cases.

Still employs DMSO by itself for flare-ups, can go without medication.

EMBODIMENTS

DMSO with Diclofenac as a treatment for arthritis.

300 ml	90% DMSO
60 ml	glycerine
25 ml	propylene glycol
100 ml	water
15 ml	ethyl alcohol
75 gm	Diclofenac

Solution as a treatment for Psoriasis

65 ml	90% DMSO
3.375 gm	Diclofenac
80 ml	H ₂ O
5 ml	2% Xylocaine
250 ml	ethyl alcohol
65 ml	glycerine
30 ml	propylene glycol
5 ml	tar

DMSO with Diclofenac & Urea as a treatment for Arthritis with added skin protection.

325 ml	DMSO 90%
70 ml	H ₂ O
50 gm	Urea
25 ml	Glycerine
75 gm	Diclofenac
25 ml	Propylene Glycol

Solution for treatment of Herpes

335 ml	DMSO 90%
25 ml	Glycerol
25 ml	Propylene glycol
100 ml	H ₂ O
15 ml	Ethyl Alcohol
75 gm	Diclofenac

The following case histories are offered where penetrating solutions according to the invention are employed.

In each of the cases set out below, the anti-inflammatories used were Naproxen or Diclofenac.

CASE 1

Mrs. E. G.-Age 58 Years-Rheumatoid Arthritis

Severe pain in left tarsal joint, then late in May, right foot then rapidly involved right leg, both shoulders, elbows, and wrists. Was first treated with phenylbutazone, then Naproxen, but four months later was becoming severely disabled with acute symptoms particularly shoulders, wrists and right foot-33 joints involved. Thereafter, treatment with penetrating solution comprising DMSO with Naproxen, Ethanol, water, propylene glycol and glycerine by the topical application thereof. Indocid was administered by mouth. By the next month some improvement in mobility, but shoulders still only slight (10) abduction. Treatment was continued five times daily. Three months later remarkable improvement in mobility. Three months later, returned to work part-time.

This patient has shown steady improvement with essentially full return to range of motion in all joints.

CASE 2

Mrs. B., W.-Age 52 Years-Post Traumatic Arthritis

Ankle-skiing accident with comminuted fracture-repaired by surgical intervention with numerous screws and plates-one screw later removed. After 13 years of restricted movement and acute pain, patient was advised that if she was not prepared to tolerate the pain—the only alternatives were fusion or amputation. Began trial with topical application of a penetrating solution of DMSO anti-inflammatories, propylene glycol, water and glycerine. Within days mobility began to improve and this was gradually followed by a reduction in pain. Four months later, almost complete return of function and was pain free. Now only employs DMSO at irregular intervals.

CASE 3

Mrs. J. F.-Age 52 years-Traumatic Arthritis

Fractured left ankle on three occasions—each repaired by open reduction. Movements severely restricted and pain severe, employed crutches—has done so for three years. Began topical treatment with formulation used in Case 1. After treatment, flexibility and comfort both improving—can bear some weight. A month later, flexibility improving but still a long way to go. However, lateral and medial movement of tarsal joints had improved considerably but dorsiflexion still quite limited. Four months later can finally touch heel to floor. Some months later, ankle greatly improved both mobility improved and pain quite tolerable—has been able to live normally, walks, dances, etc. has had bouts of gouty arthritis in other foot but this is also under satisfactory control.

CASE 4

Mr. H. B.-Age 63 Years-Arthritis

Arthritis in wrists, hands, ankle, feet and back. Arthritis recurrent exacerbations for 22 years. Has reached the point where wrists and ankles are almost completely ankylosed—very little movement obtainable is not able to continue at work. Barely able to walk—began topical application of penetrating solution comprising DMSO anti-inflammatory, propylene glycol, glycerine, water. Improvement was seen quite rapidly by reduction of effusion and slow increase of mobility over the years, in spite of exacerbations of acute arthritis, his mobility has increased until he can walk much better, lifestyle closer to normal.

CASE 5

Mr. M. L.-Age 51 Years-Osteoarthritis

Right knee, began following a football injury 30 years ago—had meniscus excised. Activities quite limited due to pain. Began topical application of penetrating solution comprising DMSO, anti-inflammatory, propylene glycol, glycerine and water. Exercise tolerance and comfort improved steadily. Patient has been able to participate in sports in more comfort.

CASE 6

Mr. K. L.-Age 62 Years-Osteoarthritis

Knees, has had one cartilage removed—unable to participate in sports without pain. Begam topical applica-

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ion of formulation used in Case 1. Increased ability to participate in sports. Improvement still maintained in spite of acute flare-ups on occasion.

CASE 7

Mr. B. P.-Age 59 years-Acute Bursitis and Arthritis

Acute Bursitis left shoulder. Abduction only 150. Acute pain in both knees from degenerated cartilages and osteoarthritis. Patient began topical treatment with penetrating solution comprising DMSO, anti-inflammatory, propylene glycol, glycerine and water after arthroscopy and by the time his surgical booking had arrived, he was so much improved he refused the surgical procedure. His pain gradually receded, mobility of knees and shoulder increased until he was able to live in comfort and return to active work and sports without pain. He now only requires occasional application of DMSO solution for slight discomfort.

CASE 8

Age 64 years

Patient diagnosed as having neuromuscular rheumatism and advised prolonged bed rest-suggested period three years. Patient has marked crepitus joints-had been told "her chances of working again were non-existent" (Mayo Clinic). Patient was a practical nurse who had re-entered a registered nursing training course but was forced to stop due to illness-when first seen was in a chair and even had great difficulty in swallowing. After treatment with penetrating solution comprising DMSO, anti-inflammatory, propylene glycol glycerine and water for several days, a slight increase in movement of joints was detectable. A month later, feels immensely better and flexion and rotation of shoulders has increased dramatically. She has an excellent response. Subsequently returned to nursing school, works three nights a week and has returned to driving an automobile. This patient has obtained full function of joints and muscles; has completed her nursing training and has worked full time since. She has now entered the B.Sc. nursing training course and is doing very well.

As many changes can be made to the embodiments disclosed without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

We claim:

1. A deep and rapidly penetrating homogeneous solution for topical application causing medicine to penetrate deeply into affected parts of the body without irritating the skin or leaving a greasy film on the skin when the solution is applied topically, the solution comprising:

- (a) between about 40% and about 85% DMSO by weight of the solution;
- (b) a polyalcohol for assisting to retain moisture in the skin and prevent the skin from dehydrating;
- (c) dispersant for assisting to disperse the components in solution to provide a homogeneous solution when applied and when penetrating the skin medicine

(e) water.

2. The solution of claim 1, wherein the medicine is Naproxen, ethanol is added as a solubilizing agent.

3. The solution of claim 1, wherein the medicine is Nifedipine.

4. The solution of claim 1, wherein the medicine is Diclofenac.

5. The solution of claim 1, wherein the polyalcohol has 3-5 carbon atoms.

6. The solution of claim 2, wherein the polyalcohol has 3-5 carbon atoms.

7. The solution of claim 3, wherein the polyalcohol has 3-5 carbon atoms.

8. The solution of claim 4, wherein the polyalcohol has 3-5 carbon atoms.

9. The solution of claim 1, wherein the polyalcohol is glycerol (glycerine).

10. The solution of claim 2, wherein the polyalcohol is glycerol (glycerine).

11. The solution of claim 3, wherein the polyalcohol is glycerol (glycerine).

12. The solution of claim 4, wherein the polyalcohol is glycerol (glycerine).

13. The solution of claim 1, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

14. The solution of claim 1, wherein the DMSO constitutes about 65% by weight of the solution.

15. The solution of claim 1, wherein the dispersant is propylene glycol.

16. The solution of claim 2, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

17. The solution of claim 2, wherein the DMSO constitutes about 65% by weight of the solution.

18. The solution of claim 2, wherein the dispersant is propylene glycol.

19. The solution of claim 3, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

20. The solution of claim 3, wherein the DMSO constitutes about 65% by weight of the solution.

21. The solution of claim 3, wherein the dispersant is propylene glycol.

22. The solution of claim 4, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

23. The solution of claim 4, wherein the DMSO constitutes about 65% by weight of the solution.

24. The solution of claim 4, wherein the dispersant is propylene glycol.

25. The solution of claim 5, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

26. The solution of claim 5, wherein the DMSO constitutes about 65% by weight of the solution.

27. The solution of claim 5, wherein the dispersant is propylene glycol.

28. The solution of claim 6, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

29. The solution of claim 6, wherein the DMSO constitutes about 65% by weight of the solution.

30. The solution of claim 6, wherein the dispersant is propylene glycol.

31. The solution of claim 7, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

32. The solution of claim 7, wherein the DMSO constitutes about 65% by weight of the solution.

33. The solution of claim 7, wherein the dispersant is propylene glycol.

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34. The solution of claim 8, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

35. The solution of claim 8, wherein the DMSO constitutes about 65% by weight of the solution.

36. The solution of claim 8, wherein the dispersant is propylene glycol.

37. The solution of claim 9, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

38. The solution of claim 9, wherein the DMSO constitutes about 65% by weight of the solution.

39. The solution of claim 9, wherein the dispersant is propylene glycol.

40. The solution of claim 10, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

41. The solution of claim 10, wherein the DMSO constitutes about 65% by weight of the solution.

42. The solution of claim 10, wherein the dispersant is propylene glycol.

43. The solution of claim 11, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

44. The solution of claim 11, wherein the DMSO constitutes about 65% by weight of the solution.

45. The solution of claim 11, wherein the dispersant is propylene glycol.

46. The solution of claim 12, wherein the DMSO is present between about 60% and about 70% by weight of the solution.

47. The solution of claim 13, wherein the DMSO constitutes about 65% by weight of the solution.

48. The solution of claim 12, wherein the dispersant is propylene glycol.

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United States Patent [19]
Sandborn

[11] Patent Number: 4,652,557
[45] Date of Patent: * Mar. 24, 1987

[54] PHARMACEUTICAL SOLUTIONS
COMPRISING DIMETHYL SULFOXIDE

[75] Inventor: Edmund Sandborn, Burlington,
Canada

[73] Assignee: Clark Pharmaceutical Laboratories
Ltd., Weston, Canada

[*] Notice: The portion of the term of this patent
subsequent to Mar. 11, 2003 has been
disclaimed.

[21] Appl. No.: 791,102
[22] Filed: Oct. 24, 1985

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 610,590, May 15,
1984, Pat. No. 4,575,515.

[51] Int. Cl.⁴ A61K 31/10; A61K 31/60;
A61K 31/605

[52] U.S. Cl. 514/164; 514/159;
514/936

[58] Field of Search 514/708, 936, 647

[56] References Cited

U.S. PATENT DOCUMENTS

3,551,554	12/1970	Herschler	424/45
3,711,602	1/1973	Herschler	424/45
3,740,420	6/1973	Herschler et al.	424/45
3,743,727	7/1973	Herschler	514/936
4,353,896	10/1982	Levy	514/936
4,369,190	1/1983	Schulte	514/936
4,575,515	3/1986	Sandborn	514/708

FOREIGN PATENT DOCUMENTS

1001075 12/1976 Canada
1005761 -2/1977 -Canada

Primary Examiner—Ronald W. Griffin
Attorney, Agent, or Firm—James D. Fornari

[57] ABSTRACT

Novel pharmaceutical solutions and particularly novel
pharmaceutical solutions comprising dimethyl sulfoxide
(DMSO).

9 Claims, No Drawings

PHARMACEUTICAL SOLUTIONS COMPRISING
DIMETHYL SULFOXIDE

FIELD OF INVENTION

This is a continuation-in-part application of U.S. application Ser. No. 06/610,590 filed May 15, 1984, now U.S. Pat. No. 4,575,515, issued Nov. 11, 1986. This invention relates to novel pharmaceutical solutions and particularly novel pharmaceutical solutions comprising dimethyl sulfoxide (DMSO).

BACKGROUND OF THE INVENTION

If one rubs a few drops of DMSO on any part of his/her person, it is usually absorbed very rapidly and a taste resembling garlic is immediately present. This finding subsequently led to a most important finding of pharmacologic ability of pure DMSO of various strengths to reduce inflammation and pain in a wide range of conditions to penetrate into the skin after topical application of DMSO for the lessening of pain and swelling of inflammation. Many clinicians have reported particularly gratifying results by the use of DMSO in the management of arthritis.

U.S. Letters Pat. No. 3,549,770, teaches the topical application of undiluted dimethyl sulfoxide, and dimethyl sulfoxide with appropriate pharmaceutical diluents, excipients and adjuvants in the treatment of tissue damage, pain, abnormal muscle contraction and vascular insufficiency.

The facility with which DMSO penetrates the skin and other membranes has spawned considerable research into the use of DMSO as a vehicle for the administration of drugs through topical application. In the course of that research a number of different products were added to DMSO with ranging degrees of success.

U.S. Pat. No. 3,711,606 teaches the use of DMSO as a carrier in concentrations of 50% and over by weight with a steroid in lotion, cream, gel and ointment forms to penetrate rapidly to and saturate the stratum corneum, the highly resistant "horny layer" of the skin which is the major barrier to penetration.

According to this patent "The Steroid continues to penetrate through the skin from this reservoir in the stratum corneum to the underlying tissue and into the circulatory system" (Column 9, line 50-53).

U.S. Pat. No. 3,711,602 also teaches the compositions (creams, suppositories, ointments and gels) for topical application for enhancing tissue penetration of physiologically active agents (for example, physiologically active steroids, antineoplastic agents, antigens, antihistamine agents, neuropharmacologic agents, anti-inflammatory agents, anticoagulants, vasodilators, ultra-violet screening agents and agents with DMSO).

However, these compositions are extremely greasy and are solely for surface penetration, very little penetrating deeply into affected areas where the greatest need arises. See also U.S. Pat. Nos. 3,551,554; 3,740,420; 3,743,727; 3,790,682; 4,369,190 and 3,499,961 and Canadian Pat. Nos. 1,001,075; 1,011,255; 1,043,704; 980,252 and 1,005,761.

Furthermore these compositions are not suitable for direct application to an afflicted part of the body (joints etc.). In addition, DMSO also captures water from the skin, being a hydroxyl ion scavenger thereby dehydrating the skin.

It is therefore, an object of this invention to provide penetrating solutions, allowing penetration deeply into

affected parts of the body, comprising DMSO, preferably another medicine which may be applied topically and which rapidly penetrates deeply into the body carrying the medication in the solutions with it while protecting the skin against dehydration.

Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of the embodiments thereof.

SUMMARY OF THE INVENTION

According to one aspect of the invention, a deeply and rapidly penetrating homogeneous solution for topical application causing medicine to penetrate deeply and rapidly into affected parts of the body without irritating the skin or leaving a greasy film on the skin when the solution is applied topically is provided, the solution comprising:

(a) between about 40% and about 85% DMSO by weight of the solution, more preferably between about 60% and about 70% DMSO by weight of the solution and most preferably about 65% DMSO by weight of the solution;

(b) a polyalcohol, preferably having 3-5 carbon atoms, for the retention of moisture in the skin, in one embodiment, glycerol or glycerine;

(c) A dispersant for assisting to disperse the components in solution to provide a homogeneous solution when applied to the skin, in one embodiment propylene glycol;

(d) a medicine for example naproxen and diclofenac dissolved in the solution;

(e) water.

Because the medicine must be dissolved in the solution, a solubilizing agent may be added to the solution to dissolve the medicament. For example, naproxen is not soluble in DMSO. Therefore, ethanol is used to solubilize also be added to the solution where desired.

When the penetrating solutions of the invention are employed in topical applications unexpected results from treatment therewith are obtained. This is because of the ability of the solution to penetrate quickly and deeply into the body through the skin and tissue below the point of topical application. Furthermore, because of the nature of the solution, the skin is not dried out. Where glycerol is employed, glycerol is a hydroxyl radical scavenger (as is DMSO) and assists in the medicinal effect of the DMSO in the solution. The dispersant propylene glycol is also a hydroxyl radical scavenger.

The formulations are prepared by combining the requisite amounts of the ingredients together (adding solubilizing agents, for example ethanol where naproxen is to be included). The medicines that may be used with the DMSO may be manufactured according to the processes taught in the following patents or other such suitable processes: NAPROXEN: Canadian Pat. Nos. 1,122,603; 1,004,226; 1,142,957; 1,137,108; 879,118; 879,719; 936,171; 955,600; 960,668; 960,689; 983,517; 991,655; 1,000,725; 1,000,726; 1,020,575; and 1,124,735. DICLOFENAC: Canadian Pat. Nos. 850,133; 811,738; 829,910; 918,175; 765,432; 827,708; 1,126,746; and 1,050,565. NIFEDIPINE: Canadian Pat. Nos. 981,582; 934,758; 868,911; 921,035; and 1,080,223. Triethanolamine salicylate may also be used.

The invention will now be illustrated having regard to the following embodiments and exemplary test cases.

EMBODIMENTS

DMSO with diclofenac as a treatment for arthritis

300 ml 90% DMSO
60 ml glycerine
25 ml propylene glycol
100 ml water
15 ml ethyl alcohol
75 gm diclofenac

Solution as a treatment for psoriasis

65 ml 90% DMSO
3.375 gm diclofenac
80 ml H₂O
5 ml 2% xylocaine
250 ml ethyl alcohol
65 ml glycerine
30 ml propylene glycol
5 ml tar

DMSO with diclofenac and urea as a treatment for Arthritis with added skin protection

325 ml DMSO 90%
70 ml H₂O
50 gm urea
25 ml glycerine
75 gm diclofenac
25 ml propylene glycol
Solution for treatment of herpes
335 ml DMSO 90%
25 ml glycerol
25 ml propylene glycol
100 ml H₂O
15 ml ethyl alcohol
75 gm diclofenac

DMSO with triethanolamine salicylate in 500 c.c. solution

315 ml 90% dimethyl sulfoxide
30 ml glycerine
55 ml propylene glycol
100 ml distilled water
52 g triethanolamine salicylate

The following case histories are offered where penetrating solutions according to the invention were employed.

In each of cases 1 to 8 inclusive the anti-inflammatory used were naproxen or diclofenac.

Case 1. Mrs. E. G.—Age 58 Years—Rheumatoid Arthritis

Severe pain in left tarsal joint, then late in May, right foot then rapidly involved right leg, both shoulders, elbows and wrists. Was first treated with phenylbutazone, then naproxen, but four months later was becoming severely disabled with acute symptoms, particularly shoulders, wrists, and right foot - 33 joints involved. Thereafter, treatment with penetrating solution comprising DMSO with naproxen, application thereof. Indocid was administered by mouth. By the next month some improvement in mobility, but shoulders still only slight (10) abduction. Treatment was continued five times daily. Three months later remarkable improvement in mobility. Three months later, returned to work part-time.

This patient has shown steady improvement with essentially full return to range of motion in all joints.

Still employs DMSO by itself for flare-ups. Can go without medication.

Case 2. Mrs. B. W.—Age 52 Years—Post Traumatic Arthritis

Ankle-skiing accident with comminuted fracture. Repaired by surgical intervention with numerous screws and plates—one screw later removed. After 13 years of restricted movement and acute pain, patient was advised that if she was not prepared to tolerate the pain, the only alternatives were fusion or amputation. Began trial with topical application of a penetrating solution of DMSO anti-inflammatories, propylene glycol, water and glycerine. Within days mobility began to improve and this was gradually followed by a reduction in pain. Four months later almost complete return of function and was pain-free. Now only employs DMSO at irregular intervals.

Case 3. Mrs. J. F.—Age 52 Years—Traumatic Arthritis

Fractured left ankle on three occasions - each repaired by open reduction. Movements severely restricted and pain severe. Employed crutches—has done so for three years. Began topical treatment with formulation used in Case 1. After treatment, flexibility and comfort both improving—can bear some weight. A month later flexibility improving but still a long way to go. However, lateral and medial movement of tarsal joints had improved considerably but dorsiflexion still quite limited. Four months later could finally touch heel to floor. Some months later, ankle greatly improved. Both mobility improved and pain quite tolerable. Has been able to live normally, walks, dances, etc. Has had bouts of gouty arthritis in other foot but this is also under satisfactory control.

Case 4. Mr. H. B.—Age 63 Years—Arthritis

Arthritis in wrists, hands, ankle, feet and back. Has reached the point where wrists and ankles are almost completely ankylosed—very little movement obtainable. Is not able to continue at work. Barely able to walk. Began topical application of penetrating solution comprising DMSO anti-inflammatory, propylene glycol, glycerin and water. Improvement was seen quite rapidly by reduction of effusion and slow increase of mobility over the years. In spite of exacerbations of acute arthritis his mobility has increased until he can walk much better. Lifestyle closer to normal.

Case 5. Mr. M. L.—Age 51 Years—Osteoarthritis

Right knee—began following a football injury 25 years ago. Had meniscus excised. Activities quite limited due to pain. Began topical application of penetrating solution comprising DMSO, anti-inflammatory propylene glycol, glycerine and water. Exercise tolerance and comfort improved steadily. Patient has been able to participate in sports in more comfort.

Case 6. Mr. K. L.—Age 62 Years—Osteoarthritis

Knees. Has had one cartilage removed. Unable to participate in sports without pain. Began topical application of formulation used in Case 1. Increased ability to participate in sports. Improvement still maintained in spite of acute flare-ups on occasion.

Case 7. Mr. B. P.—Age 59 Years—Acute Bursitis and Arthritis

Acute Bursitis left shoulder. Abduction only 150. Acute pain in both knees from degenerated cartilages and osteoarthritis. Patient began topical treatment with penetrating solution comprising DMSO, anti-inflammatory, propylene glycol, glycerine and water after arthroscopy and by the time his surgical booking had arrived, he was so much improved he refused the surgical procedure. His pain gradually receded, mobility of knees and shoulder increased until he was able to live in comfort and return to active work and sports without pain. He now only requires occasional application of DMSO solution for slight discomfort.

Case 8. Age 64 Years

Patient diagnosed as having neuromuscular rheumatism and advised prolonged bed rest—suggested period, three years. Patient has marked crepitus joints. Had been told 'her chances of working again were non-existent' (Mayo Clinic). Patient was a practical nurse who had re-entered a registered nursing training course but was forced to stop due to illness. When first seen was in a wheel chair and even had great difficulty in swallowing. After treatment with penetrating solution comprising DMSO, anti-inflammatory, propylene glycol, glycerin and water for several days, a slight increase in movement of joints was detectable. A month later, felt immensely better and flexion and rotation of shoulders had increased dramatically. She had an excellent response. Subsequently returned to nursing school. Works three nights a week and has returned to driving an automobile. This patient has obtained full function of joints and muscles. Has completed her nursing training and has worked full-time since. She has now entered the B.Sc. nursing training course and is doing very well.

Case 9

Patient was diagnosed as having chondromalacia and osteoarthritis in the knee of many years duration. She had considerable limitation of movement and pain. Crepitations felt on knee movements. After treatment with penetrating solution comprising dimethyl sulfoxide, triethanolamine salicylate, glycerine, propylene glycol and distilled water for about four months, the knee was greatly improved and pain relieved. While the knee was still slightly stiff, mobility was greatly improved. Her knee was still slightly affected by the weather.

Case 10

Patient was diagnosed as having arthritis in her left knee of many years duration. After treatment with the penetrating solution comprising dimethyl sulfoxide, triethanolamine salicylate, glycerine, propylene glycol and distilled water, there was a very marked improvement over the first four months. Now she uses the solution on a prn basis.

Case 11

Patient was in extreme pain from post herpetic neuritis. She had a band of scars C8 to T3—medial arm, back axilla and upper breast. Patient had a previous history of Graves Disease and cancer of the bladder. After treatment with the penetrating solution of dimethyl sulfoxide, triethanolamine salicylate, glycerine, propylene glycol and distilled water, within two weeks there was

great improvement of post herpetic neuritis. After one week only itchiness and tenderness remained.

Case 12

Patient was diagnosed as having post herpetic neuritis left forearm and hand. She had had this condition for seven years duration. After treatment with a penetrating solution of dimethyl sulfoxide, diclofenac, glycerine, propylene glycol, and distilled water, there was considerable improvement. However, after treatment with the penetrating solution of dimethyl sulfoxide, triethanolamine salicylate, glycerine, propylene glycol and distilled water, there were excellent results.

Case 13

Patient was diagnosed as having rheumatoid arthritis since 1974. The patient had extreme deformity of the wrists, hands, knees and elbows with rheumatoid nodules on forearms and elbows. After treatment with both (a) dimethyl sulfoxide, diclofenac, glycerine, propylene glycol, and distilled water and (b) dimethyl sulfoxide, triethanolamine salicylate, glycerine, propylene glycol, and distilled water, great improvement in mobility and comfort was the result. He has returned to work as a furniture restorer, something he was unable to do for some time before the treatments.

Case 14

The patient, a former football player, was diagnosed as having osteoarthritis of the knee and ankle, chondromalacia. The patient had arthroscopic removal of part of his semilunar cartilages. He was in extreme pain, unable to continue playing golf or other activities for a period of at least two years prior to treatment. After treatment with dimethyl sulfoxide, triethanolamine salicylate, glycerine, propylene glycol, and distilled water, even though there was X-ray evidence of moderate degeneration of knee cartilages, he has improved his range of mobility and comfort to the extent that he is now able to golf 18 holes regularly.

As many changes can be made to the embodiments disclosed without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

The embodiments of the invention in which an exclusive property or privilege is claimed are as follows:

1. A deep and rapidly penetrating homogeneous solution for topical application causing medicine to penetrate deeply into affected parts of the body without irritating the skin or leaving a greasy film on the skin when the solution is applied topically, the solution comprising:

- (a) between about 40% and about 85% DMSO by weight of the solution;
- (b) a polyalcohol for assisting to retain moisture in the skin and prevent the skin from dehydrating;
- (c) a dispersant for assisting to disperse the components in the solution to provide a homogeneous solution when applied and when penetrating the skin;
- (d) triethanolamine salicylate;
- (e) water.

2. The solution of claim 1, wherein the polyalcohol has 3 to 5 carbon atoms.

3. The solution of claim 1, wherein the polyalcohol is glycerol (glycerine).

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- 4. The solution of claim 3, wherein the DMSO is present between about 60% and about 70% by weight of the solution.
- 5. The solution of claim 3, wherein the DMSO constitutes about 65% by weight of the solution.
- 6. The solution of claim 3 wherein the dispersant is propylene glycol.
- 7. The solution of claim 1, wherein the DMSO is

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- present between about 60% and about 70% by weight of the solution.
- 8. The solution of claim 1, wherein the DMSO constitutes about 65% by weight of the solution.
- 9. The solution of claim 1, wherein the dispersant is propylene glycol.

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ITEM 14: PATENT CERTIFICATION

21 CFR 314.50 (i)

Time Sensitive Patent pursuant to 21 CFR 314.53 for NDA 20-947

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: PENNSAID® Topical Solution (1.5% w/w diclofenac sodium)
Active Ingredient: diclofenac sodium
Strength: 1.5% w/w
Dosage Form: Topical solution
Approval Date: This product is the subject of this application for which approval is being sought.

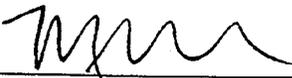
U.S. Patent Number: 4,575,515 (March 11, 1986)
Expiration Date: March 11, 2006
Type of Patent: Drug Product (Composition/Formulation)
Name of Patent Owner: Dimethaid Research Inc.
U.S. Agent: Dr. Frederick Ballantyne, Dimethaid International Inc. (a wholly-owned subsidiary of Dimethaid Research Inc.)

U.S. Patent Number: 4,652,557 (March 24, 1987)
Expiration Date: March 24, 2007
Type of Patent: Drug Product (Composition/Formulation)
Name of Patent Owner: Dimethaid Research Inc.
U.S. Agent: Dr. Frederick Ballantyne, Dimethaid International Inc. (a wholly-owned subsidiary of Dimethaid Research Inc.)

The undersigned declares that the above stated United States Patent Numbers 4,575,515 and 4,652,557 cover the composition and formulation of PENNSAID® Topical Solution. This product is the subject of this application for which approval is being sought.

Dated, this 7th day of August, 2001.

DIMETHAID INTERNATIONAL INC.

Per: 
Rebecca E. Keeler,
Director

EXCLUSIVITY SUMMARY

NDA # 020947

SUPPL #

HFD # 170

Trade Name Pennsaid topical solution

Generic Name diclofenac sodium

Applicant Name Nuvo Research

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-201 Voltaren

NDA# 21-005 Solaraze

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies PEN-03-112 and RA-CP-109-US

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Studies PEN-03-112 and RA-CP-109-US

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 42,773 YES ! NO
! Explain:
Nuvo/Dimethaid was identified as the sponsor.

Investigation #2 !
IND # 42,773 YES ! NO
! Explain:
Nuvo/Dimethaid was identified as the sponsor.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Robert Shibuya, MD
Title: Clinical Team Leader, DAARP
Date: 10-28-09

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Director, DAARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

JESSICA M BENJAMIN
10/29/2009

SHARON H HERTZ
10/29/2009



NUVO

Claimed Exclusivity 21 CFR 314.50 (j)

Pursuant to 21 CFR 314.108, the applicant, Nuvo Research Inc., is hereby claiming exclusivity under Section 314.108(b)(4), for PENNSAID[®] Topical Solution (diclofenac sodium topical solution) 1.5% w/w. Nuvo Research Inc. is submitting the following information to show that the application contains "new clinical investigations" that are "essential to approval of the application" and were "conducted or sponsored by the applicant":

i) New Clinical Investigations:

The Applicant, NUVO RESEARCH INC., hereby certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in Section 314.108(a).

ii) Essential to approval:

The Applicant, NUVO RESEARCH INC., hereby certifies that it has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigations in the application.

iii) Conducted or sponsored by:

The Applicants wholly-owned subsidiary, Dimethaid International Inc., was the sponsor named in the Form FDA-1571 for IND 42,773, under which the new clinical investigations that are essential to the approval of its application were conducted.

Dated, this 26 day of January, 2009.

NUVO RESEARCH INC.

Per: _____

John London
Vice Chairman



DIMETHAID INTERNATIONAL INC.

Regulatory Affairs Department
10 - 7560 Airport Road
Mississauga, Ontario, CANADA, L4T 4H4
Tel.: (905) 673-6980 Fax: (905) 673-0127

**Claimed Exclusivity
21 CFR 314.50 (j)**

Pursuant to 21 CFR 314.108, the applicant, Dimethaid International Inc., a fully-owned subsidiary of Nuvo Research Inc., is hereby claiming exclusivity under Section 314.108(b)(4), for PENNSAID® Topical Solution (1.5% w/w diclofenac sodium). Dimethaid International Inc. is submitting the following information to show that the application contains "new clinical investigations" that are "essential to approval of the application" and were "conducted or sponsored by the applicant":

i) New Clinical Investigations:

The applicant, DIMETHAID INTERNATIONAL INC., hereby certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in Section 314.108(a).

ii) Essential to approval:

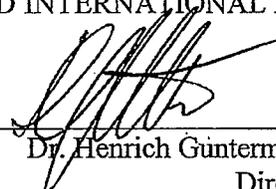
The applicant, DIMETHAID INTERNATIONAL INC., hereby certifies that it has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigations in the application.

iii) Conducted or sponsored by:

The applicant, Dimethaid International Inc., was the sponsor named in the Form FDA-1571 for IND 42,773, under which the new clinical investigations that are essential to the approval of its application were conducted.

Dated, this 23 day of June, 2006.

DIMETHAID INTERNATIONAL INC.

Per: 

Dr. Henrich Güntermann,
Director

ITEM 19: Claimed Exclusivity

21 CFR 314.50 (j)

Claimed Exclusivity
21 CFR 314.50 (j)

Pursuant to 21 CFR 314.108, the applicant, Dimethaid International Inc., is hereby claiming exclusivity under Section 314.108(b)(4), for PENNSAID[®] Topical Solution (1.5% w/w diclofenac sodium).

Dimethaid International Inc. is submitting the following information to show that the application contains "new clinical investigations" that are "essential to approval of the application" and were "conducted or sponsored by the applicant":

i) New Clinical Investigations:

The applicant, DIMETHAID INTERNATIONAL INC., hereby certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in Section 314.108(a).

ii) Essential to approval:

The applicant, DIMETHAID INTERNATIONAL INC., hereby certifies that it has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigations in the application.

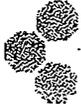
iii) Conducted or sponsored by

The applicant, Dimethaid International Inc., was the sponsor named in the Form FDA-1571 for IND 42,773, under which the new clinical investigations that are essential to the approval of its application were conducted.

Dated, this 7TH day of August, 2001.

DIMETHAID INTERNATIONAL INC.

Per: 
Rebecca E. Keeler,
Director



NUVO

NDA 020-947

New Drug Application

PENNSAID[®] Topical Solution
(diclofenac sodium topical solution) 1.5% w/w

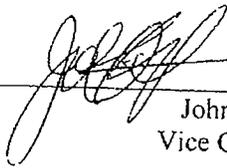
DEBARMENT CERTIFICATION

The Applicant, Nuvo Research Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with application NDA 020-947 for PENNSAID[®] Topical Solution (diclofenac sodium topical solution) 1.5% w/w.

Dated, this 26 day of January, 2009.

NUVO RESEARCH INC.

Per: _____


John London
Vice Chairman



DIMETHAID INTERNATIONAL INC.

Regulatory Affairs Department
10 - 7560 Airport Road
Mississauga, Ontario, CANADA, L4T 4H4
Tel.: (905) 673-6980 Fax: (905) 673-0127

NDA 020-947

New Drug Application

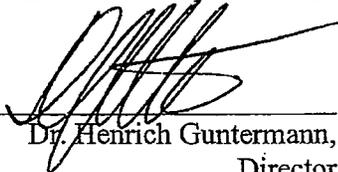
PENNSAID® Topical Solution
(1.5% w/w diclofenac sodium)

DEBARMENT CERTIFICATION

The applicant, Dimethaid International Inc., a fully-owned subsidiary of Nuvo Research Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with application NDA 020-947 for PENNSAID® Topical Solution (1.5% w/w diclofenac sodium).

Dated, this 23 day of June, 2006.

DIMETHAID INTERNATIONAL INC.

Per: 

Dr. Henrich Guntermann,
Director



DIMETHAID INTERNATIONAL INC.

NDA #20-947

New Drug Application

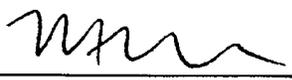
PENNSAID® Topical Solution
(1.5% w/w diclofenac sodium)

DEBARMENT CERTIFICATION

The applicant, DIMETHAID INTERNATIONAL INC., hereby certifies that it did not and will not use in any capacity the services of any individuals or firms debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with application No.20-947 for PENNSAID® Topical Solution.

Dated, this 7th day of August, 2001.

DIMETHAID INTERNATIONAL INC.

Per: 
Rebecca E. Keeler,
Director

DEBARMENT CERTIFICATION

The applicant, DIMETHAID RESEARCH INC., hereby certifies that in connection with the attached New Drug Submission for Pennsaid™, it did not and will not use in any capacity, the services of any individuals or firms that have been debarred by the Food and Drug Administration.

Dated, this *15th* day of December, 1997

DIMETHAID RESEARCH INC.

Per: 

Rebecca E. Keeler,
President and CEO.

From: Greeley, George
To: Benjamin, Jessica;
CC: Stowe, Ginneh D.;
Subject: NDA ——— Pennsaid
Date: Thursday, July 09, 2009 9:12:00 AM
Attachments:

b(4)

Hi Jessica,

The Pennsaid (diclofenac sodium) full waiver was reviewed by the PeRC PREA Subcommittee on July 08, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children. The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

 Please consider the environment before printing this e-mail.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

DIMETHAID
RESEARCH INC

PENNSAID(DICLOFENAC
SODIUM)1.5% TOP LOTI

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/s/

JESSICA M BENJAMIN
10/30/2009

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: NDA20-947:Pennsaid
Date: Tuesday, November 03, 2009 11:13:05 AM
Attachments: FINAL label 11 3 09.doc
REMS Appendix C and D (2).pdf
11 02 09 Pennsaid IFU DRISK Appendix B clean copy 11 09.doc
clean REMS Appendix C and D (2).doc

Hi Mimi,

I have attached the final agreed-upon label. We updated the highlights section to reflect the changes within the PI.

I have also attached your proposed REMS and Patient Information for Use. We reformatted the REMS to match the information you submitted on October 26th. Please review the changes and recommendations and let me know if you have any questions. There is a pdf version of the REMS with comments as well as a clean copy. Your immediate response is necessary since the PDUFA date is tomorrow.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Tuesday, November 03, 2009 9:51 AM
To: Benjamin, Jessica
Subject: NDA20-947:Pennsaid

Good morning, Jessica,

I just want to confirm that you have received everything that you have requested from us and there is nothing else that you're waiting for. Please let us know.

Have a good day,

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

PMR/PMC Development Template

NDA # 20-947

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Evaluation of the potential carcinogenicity of DMSO in a 2-year bioassay in the rat

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	already submitted
Study/Clinical trial Completion Date:	<u>July 31, 2011</u>
Final Report Submission Date:	<u>August 31, 2012</u>
Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

DMSO, a solvent excipient used in PENNSAID Topical Solution, has never been evaluated appropriately for carcinogenicity. Data from chronic toxicology studies conducted in rat and minipig did not reveal signs of pre-neoplasia related to this compound.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This PMR is to investigate a potential for risk of tumorigenicity related to the excipient DMSO contained in Pennsaid.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Non-clinical study in a 2-year bioassay in the rat.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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
11/03/2009

LARISSA LAPTEVA
11/03/2009

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Non-clinical Fertility and Early Embryonic Development study in the rat.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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
11/03/2009

LARISSA LAPTEVA
11/03/2009

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Nonclinical Pre- and Postnatal Development Study in the rat.
--

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

NUVO RESEARCH
INC

PENNSAID(DICLOFENAC
SODIUM)1.5% TOP LOTI

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

/s/

JESSICA M BENJAMIN
11/03/2009

LARISSA LAPTEVA
11/03/2009

From: Duvall Miller, Beth A
To: Benjamin, Jessica;
CC: Quaintance, Kim M;
Subject: RE: NDA 20-947 - cleared for action
Date: Tuesday, November 03, 2009 11:06:07 AM
Attachments:

Hi Jessica,

Good news: I heard from OCC and you are cleared for action (again) from a b(2) perspective.

Thanks for your responsiveness to our questions.

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

From: Benjamin, Jessica
Sent: Tuesday, November 03, 2009 10:52 AM
To: Duvall Miller, Beth A
Subject: FW: NDA 20-947: b2 clearance questions
Importance: High

Hi Beth,

Is there any news on whether or not the lawyers have made a determination on the Pennsaid application yet?

Thanks for your help.

Jessica

From: Quaintance, Kim M

Sent: Friday, October 30, 2009 12:48 PM

To: Benjamin, Jessica

Cc: Duvall Miller, Beth A; Jani, Parinda; Stradley, Sara; Ripper, Leah W; Weiner, Janice; Dettelbach, Kim; Boocker, Nancy; Dickinson, Elizabeth; Rappaport, Bob A

Subject: RE: NDA 20-947: b2 clearance questions

Importance: High

Jessica,

I hate to do this, but this application is no longer cleared for action from a (b)(2) perspective. Additional questions have been raised by ORP and OCC regarding the _____ and they wish to look at this further. If additional information is requested, we will notify you immediately.

b(5)

We will make every effort to clear this before the November 4 PDUFA date. Please note that I will be on travel next week; therefore, after today, Beth will manage the clearance of your application.

Kim

From: Quaintance, Kim M

Sent: Thursday, October 29, 2009 8:55 AM

To: Quaintance, Kim M; Benjamin, Jessica

Cc: Duvall Miller, Beth A; Jani, Parinda; Stradley, Sara; Ripper, Leah W

Subject: RE: NDA 20-947: b2 clearance questions

Jessica (not Jennifer - sorry!)

You are cleared for action from a (b)(2) perspective.

Regards,

Kim

From: Quaintance, Kim M

Sent: Wednesday, October 28, 2009 2:07 PM

To: Benjamin, Jessica

Cc: Duvall Miller, Beth A; Jani, Parinda; Stradley, Sara; Ripper, Leah W

Subject: RE: NDA 20-947: b2 clearance questions

Hi Jennifer,

In the future, we need a little more notice for clearance. We try to keep track of all of the goal dates to keep ahead of the game, but it

is a difficult task. We meet with ORP and OCC every two weeks; we met with them Monday and will not be meeting with them again until November 9 to go over pending applications.

I will circulate this via email so that we can work out any remaining issues in time for your PDUFA date.

Stay tuned.

Kim

From: Benjamin, Jessica

Sent: Tuesday, October 27, 2009 3:22 PM

To: Quaintance, Kim M

Subject: FW: NDA 20-947: b2 clearance questions

Hi Kim,

I noticed Beth was on leave, so I am also forwarding our responses to you.

Thanks,

Jessica

From: Benjamin, Jessica

Sent: Tuesday, October 27, 2009 3:21 PM

To: Duvall Miller, Beth A

Cc: Benjamin, Jessica

Subject: RE: NDA 20-947: b2 clearance questions

Hi Beth,

We had a Major Amendment for NDA 20-947, so we never answered your 505(b)2 questions before the clock extension. Our new PDUFA date is November 4th.

Please see our responses in red below.

Let me know if you need any additional information.

Thanks,

Jessica

From: Duvall Miller, Beth A

Sent: Monday, August 03, 2009 5:18 PM

To: Benjamin, Jessica

Cc: Quaintance, Kim M

Subject: RE: NDA 20-947: b2 clearance questions

Importance: High

Hi Jessica,

We discussed your application at today's clearance meeting and do have some follow-up questions that

must be addressed before we can clear your application for action. They are:

Voltaren Gel, NDA 22-122, was approved 10/17/07 for the relief of the pain of osteoarthritis of joints amenable to topical treatment, and received 3 years of exclusivity.

b(5)

b(5)

That's it for now. We recognize that tomorrow is your due date but we must address these questions ASAP.

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

From: Benjamin, Jessica
Sent: Wednesday, July 08, 2009 2:12 PM
To: Duvall Miller, Beth A

Subject: RE: NDA 20-947: b2 assessment needed for clearance

Hi Beth,

Please find the attached b2 assessment for NDA 20-947. Let me know if you need any additional information.

<< File: NDA 20947_505b2 assessment.doc >>

Thanks,

Jessica

From: Duvall Miller, Beth A

Sent: Thursday, July 02, 2009 12:37 PM

To: Benjamin, Jessica

Subject: NDA 20-947: b2 assessment needed for clearance

Hi Jessica,

I work in the immediate office with Kim Quaintance – we track and clear 505(b)(2) applications. Your above noted 505(b)(2) application is nearing the top of our queue. We have your due date as 8/4/09 – is that correct? Are you planning an early action, if so when? What action are you planning?

Finally, in order to initiate the clearance process, we need your draft b(2) assessment which you can access here under “Internal documents for RPMs”: <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html>

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

NUVO RESEARCH
INC

PENNSAID(DICLOFENAC
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/s/

JESSICA M BENJAMIN
11/03/2009

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: Revised pennsaid label
Date: Friday, October 30, 2009 4:30:42 PM
Attachments: clean sponsor label 10_30 FDA edits.doc
label 10_30 FDA edits.pdf

Mimi,

I have attached our revised pdf version of the Pennsaid label with our changes and a clean copy with our changes accepted. Due to the upcoming PDUFA date, we request a prompt response.

Regards,

Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Friday, October 30, 2009 1:14 PM
To: Benjamin, Jessica
Subject: FW: Revised pennsaid label
Importance: High

Dear Dr. Hertz:

Once again, we would like to thank you for your time and assistance Wednesday regarding the PENNSAID Topical Solution labeling and the revised FDA label received yesterday. We are in agreement with almost all of the edits in the 10-29-09 FDA version and any additional edits are in tracking (see sections 6.1, 7, 8.1, 11, 14.1 and 16).

As a follow-up to our teleconference, we are submitting a revised adverse event table (see Table 1, Section 6.1) to address the Agency's concerns regarding the clarity of certain terms. During the call, we indicated that we would submit the revised safety table for your review and that we would consider any further suggestions from you and your team after you have reviewed our revised table.

In addition, we are also submitting a revised Table 3 (see section 14.1 *Clinical Trials* section) for your consideration. Our revisions to this section include the data from the 5-arm Phase 3 study in the table to provide full transparency of trial 112. We understand that there may be aspects of this table not presently acceptable to FDA. We are not clear on either the exact issue or the remedy. We would like to understand what additional information, if any, is needed, either at this time or in a future labeling supplement, that would allow comparison of Pennsaid with both 1) the combination regimen of oral diclofenac and Pennsaid, and 2) oral diclofenac alone.

Thank you in advance for your time in reviewing these proposed changes. We look forward to hearing from you soon.

Kind regards,

Mimi Brennan
Director, Regulatory Affairs

Nuvo Research Inc.

From: Mimi Brennan
Sent: Thursday, October 29, 2009 5:06 PM
To: Brad Galer; Dan Chicoine; John London
Cc: Michelle Hershoran; Rosemary Kerwin
Subject: FW: Revised pennsaid label
Importance: High

All,

Here's the revised label from FDA.

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Thursday, October 29, 2009 4:42 PM
To: Mimi Brennan
Cc: Benjamin, Jessica
Subject: Revised pennsaid label

Mimi,

I have attached the revised pdf version of the Pennsaid label with our changes and a clean copy with our changes accepted. Review the updated label and make any edits to the clean copy with track changes. Please note that the label has not been finalized by senior management. Due to the upcoming PDUFA date, we request a prompt response to this request.

<<clean version_FDA label 10_29_09.doc>> <<FDA label 10_29_09 track changes.pdf>>

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: Revised pennsaid label
Date: Thursday, October 29, 2009 4:42:26 PM
Attachments: clean version FDA label 10 29 09.doc
FDA label 10 29 09 track changes.pdf

Mimi,

I have attached the revised pdf version of the Pennsaid label with our changes and a clean copy with our changes accepted. Review the updated label and make any edits to the clean copy with track changes. Please note that the label has not been finalized by senior management. Due to the upcoming PDUFA date, we request a prompt response to this request.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

MEMORANDUM OF TELECON

DATE: July 28, 2009

APPLICATION NUMBER: NDA 20-947

BETWEEN:

Name: Dan Chicoine
Brad Galer
Mimi Brennan
John London
Jonathon Wilkin
Representing: Nuvo Research

Mark Mannebach
Representing: Covidien, Licensee

AND

Name: Bob Rappaport
Jessica Benjamin
DAARP, HFD-170

SUBJECT: Pennsaid review update

Dr. Rappaport conveyed to the sponsor that a final decision has not been made regarding the Pennsaid application. Dr. Rappaport also commented that the review team has fulfilled their responsibilities under the GRMP regulations to alert the sponsor of any issues during the review cycle. The sponsor always has the option of submitting additional analyses and justifications to the NDA for review. Unfortunately, under the current timeline, there is not enough time to review additional submissions although there is the option of extending the PDUFA date. Dr. Rappaport stressed to the sponsor that we have our Pharm-Tox experts currently working on the application.

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

DIMETHAID
RESEARCH INC

PENNSAID(DICLOFENAC
SODIUM)1.5% TOP LOTI

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/s/

JESSICA M BENJAMIN
10/29/2009

MEMORANDUM OF TELECON

DATE: July 23, 2009

APPLICATION NUMBER: NDA 20-947

BETWEEN:

Name: Dan Chicoine
Brad Galer
Mimi Brennan
John London
Jagat Singh
Representing: Nuvo Research

Mark Mannebach
Michael Giuliani
Chuck Finn
Frank Hurley
Representing: Covidien, Licensee

AND

Name: Adam Wasserman
Jessica Benjamin
DAARP, HFD-170

SUBJECT: Pharm-Tox recommendation

Dr. Wasserman conveyed to the sponsor that the Nonclinical reviews have been completed and they can not recommend approval of Pennsaid at this time. There are two main reasons why Dr. Wasserman is recommending a Complete Response: 1. The FDA needs results of the completed carcinogenicity study, and 2. Potential leeching of the extractables from the label onto the patients' hands. Dr. Wasserman stressed that Dr. Rappaport has not completed his review and not made a final determination of a Complete Response action.

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products

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

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/s/

JESSICA M BENJAMIN
10/29/2009

MEMORANDUM OF TELECON

DATE: June 19, 2009

APPLICATION NUMBER: NDA 20-947

BETWEEN:

Name: Dan Chicoine
Brad Galer
Jagat Singh
Mimi Brennan
John London
Michelle Hershoran
Fred Reno
Jon Daniels
Jon Wilkin
David Lin
Alan Hendricker
Representing: Nuvo Research

AND

Name: Adam Wasserman
Steve Leshin
Danae Christodoulou
Olen Stephens
Jessica Benjamin
DAARP, HFD-170

SUBJECT: SUBJECT OF TELEPHONE CONVERSATION

Dr. Wasserman, Pharm-Tox Team Leader, led the teleconference and indicated that this was an informational call only and not a decisional call. The lymphoma fatalities from the rat study may play a role in whether or not the FDA will require the full carcinogenicity study prior to approval. P/T reviewers are currently debating this issue. FDA does not believe that the nephroblastoma seen in the 13-week rat study are unrelated to DMSO. The lymphoma is a problem since they are a rare spontaneous tumor in this strain of rates, over this time period but there is no clear dose-response. Our statistical review team did not agree with the sponsor's method of analysis. FDA encouraged the sponsor to submit its best argument but warned that there are tight deadlines. The Associate Director of P/T will review any new scientific arguments submitted, which doesn't usually occur in a normal review cycle. Dr. Wasserman emphasized that the Division Director is still review the submission and has not yet made a decision.

Dr. Stephens, CMC reviewer, expressed concern that the — extractables from the label could potentially leach during product use in to the hand of the user. The sponsor was requested to

b(4)

provide data or design an experiment in order to address the concern. FDA is concerned that the product could leach onto patients' hands since the sponsor observed some leaking and label smudge during their stability study. FDA agreed that we would be willing to help with the study design.

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products

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

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/s/

JESSICA M BENJAMIN
10/29/2009

MEMORANDUM OF TELECON

DATE: May 18, 2009

APPLICATION NUMBER: NDA 20-947

BETWEEN:

Name: Dan Chicoine
Representing: Nuvo Research

Name: Dr. Brad Galer
Representing: Nuvo Research

AND

Name: Dr. Bob Rappaport
DAARP, HFD-170

Name: Jessica Benjamin
DAARP, HFD-170

SUBJECT: SUBJECT OF TELEPHONE CONVERSATION

Dr. Rappaport explained to the sponsor that the FDA is obligated, under the GRMP policies, to alert the sponsor of any potential review issues that would affect taking an action. At this point, the review team does not have any definitive issues for approvability. Dr. Rappaport explained that we are still exploring the DMSO issue but at this point we have no questions and no conclusions. Dr. Rappaport also emphasized that we are not holding back any information and we are mandated to let you know if there is an approvability issue.

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

DIMETHAID
RESEARCH INC

PENNSAID(DICLOFENAC
SODIUM)1.5% TOP LOTI

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/s/

JESSICA M BENJAMIN
10/29/2009

From: Quaintance, Kim M
To: Quaintance, Kim M; Benjamin, Jessica;
CC: Duvall Miller, Beth A; Jani, Parinda; Stradley, Sara; Ripper, Leah W;
Subject: RE: NDA 20-947: b2 clearance questions
Date: Thursday, October 29, 2009 8:54:42 AM
Attachments:

Jessica (not Jennifer - sorry!)

You are cleared for action from a (b)(2) perspective.

Regards,
Kim

From: Quaintance, Kim M
Sent: Wednesday, October 28, 2009 2:07 PM
To: Benjamin, Jessica
Cc: Duvall Miller, Beth A; Jani, Parinda; Stradley, Sara; Ripper, Leah W
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Stay tuned.

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Let me know if you need any additional information.

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Importance: High

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We discussed your application at today's clearance meeting and do have some follow-up questions that must be addressed before we can clear your application for action. They are:

Voltaren Gel, NDA 22-122, was approved 10/17/07 for the relief of the pain of osteoarthritis of joints amenable to topical treatment, and received 3 years of

b(5)

b(5)

That's it for now. We recognize that tomorrow is your due date but we must address these questions ASAP.

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

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Finally, in order to initiate the clearance process, we need your draft b(2) assessment which you can access here under “Internal documents for RPMs”: <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html>

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

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

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/s/

JESSICA M BENJAMIN
10/29/2009

505(b)(2) ASSESSMENT

Application Information		
NDA # 20-947	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Pennsaid Established/Proper Name: diclofenac sodium Dosage Form: topical solution Strengths: 1.5% w/w		
Applicant: Nuvo Research, Inc.		
Date of Receipt: February 4, 2009		
PDUFA Goal Date: August 4, 2009		Action Goal Date (if different):
Proposed Indication(s): For the treatment of the symptoms of osteoarthritis of the knee(s)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Voltaren tablets	Diclofenac safety
Published literature – Aguera 2005	Diclofenac phototransformation
Published literature – Benigni 2006 Published literature – Streicher 2004	Carcinogenicity and mutagenicity Dermal carcinogenicity
Published literature – Galmier 2005 Published literature – Poiger 2001	Diclofenac photostability Photostability and photodegradation data

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Safety and efficacy studies of Pennsaid vs oral diclofenac

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Voltaren tablets	19-201	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides a change in dosage form, from tablet to topical solution.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 5,639,738

5,852,002 (claims 1,5,6,7,10, and 11)

5,929,048 (claims 1,5,6, and 7)

Method(s) of Use/Code(s): U-402: Treatment of actinic keratoses

15) Complete the following checklist *ONLY* for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,792,753

5,852,002 (claims 2,3,4,8,9)

5,914,322

5,929,048 (claims 2,3,4)

5,985,850

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): February 5, 2009 and February 6, 2009

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

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

/s/

JESSICA M BENJAMIN
10/29/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 20-947 BLA#	NDA Supplement #-S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: PENNSAID® Topical Solution (1.5% w/w diclofenac sodium) Established/Proper Name: diclofenac sodium Dosage Form: topical solution Strengths: 1.5% w/w diclofenac sodium solution		
Applicant: Nuvo Research Inc. Agent for Applicant (if applicable): Brad Galer		
Date of Application: February 4, 2009 Date of Receipt: February 4, 2009 Date clock started after UN:		
PDUFA Goal Date: August 4, 2009	Action Goal Date (if different): <i>clock extension</i>	
Filing Date: N/A Date of Filing Meeting: N/A		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): treatment of the signs and symptoms of osteoarthritis of the knee(s)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 42,773	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments: # of years not specified</p>	<p><input checked="" type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p>Format and Content</p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES 6/5/2000 Date(s): <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 12, 2009

NDA/BLA #: NDA 20-947

PROPRIETARY/ESTABLISHED NAMES: PENNSAID® Topical Solution (1.5% w/w diclofenac sodium)

APPLICANT: Nuvo Research, Inc.

BACKGROUND: 3rd cycle review; response to 2006 approvable letter
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Rob Shibuya		Y
Clinical	Reviewer:	Nick Olmos-Lau	
	TL:		
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		



Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Steve Leshin	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Olen Stephens	Y
	TL:	Danae Christidoulou	Y
Facility (for BLAs/BLA supplements)	Reviewer:		
	TL:		
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Bob Rappaport, Sharon Hertz

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Bob Rappaport</p> <p>GRMP Timeline Milestones: PDUFA – August 4, 2009</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>
<input type="checkbox"/>	<p>If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<input type="checkbox"/>	<p>If BLA or priority review NDA, send 60-day letter.</p>
<input type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Other</p>

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

JESSICA M BENJAMIN
10/28/2009

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 20947/000	Sponsor:	DIMETHAID RES
Code:	170		L3R 3J9
Priority:	3S		MARKHAM, ONTARIO, CANADA
Stamp Date:	16-DEC-1997	Brand Name:	PENNSAID(DICLOFENAC SODIUM)1.5% TOP LOTI
PDUFA Date:	04-NOV-2009	Estab. Name:	
Action Goal:		Generic Name:	DICLOFENAC SODIUM
District Goal:	08-SEP-1998	Product Number; Dosage Form; Ingredient; Strengths	001; LOTION; DICLOFENAC SODIUM; 1.5%/1GM

FDA Contacts:	J. BENJAMIN	Project Manager	(HFD-170)	301-796-3924
	O. STEPHENS	Review Chemist	(HFD-170)	301-796-3901
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 04-AUG-2009	by M. STOCK	(HFD-320)	301-796-4753
	ACCEPTABLE	on 29-AUG-2006	by S. ADAMS	()	301-827-2443
	ACCEPTABLE	on 25-JUL-2002	by S. ADAMS	()	301-827-2443
	WITHHOLD	on 21-OCT-1998	by DAMBROGIOJ		

Establishment:	CFN: 9615349	FEI:	
	DIMETHAID RESEARCH INC 3655 CHEMIN DE LA COTE BISSONNETTE VARENNES, , CANADA		
No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER		
Profile:	LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS,	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-JUL-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: Pennsaid NDA 20-947: URGENT REQUEST
Date: Friday, July 24, 2009 4:28:36 PM
Attachments:

Hi Mimi,

I have received your email and forwarded it to the appropriate people. Dr. Rappaport is available for a short teleconference on Tuesday, July 28th, at 10:30am. Be advised that Dr. Rappaport will listen but will not be able to provide any responses since he has not completed his review at this time.

Please confirm time and forward a phone number where we can reach you then.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Friday, July 24, 2009 3:00 PM
To: Benjamin, Jessica
Subject: Pennsaid NDA 20-947: URGENT REQUEST
Importance: High

Hi Jessica,

Thank you for setting up the phone call with Dr. Wasserman yesterday.

As you are aware this matter is extremely important to Nuvo and we have serious issues we would like to discuss with Dr. Rappaport before the issuance of an action letter. More specifically, we are sending a proposal which is attached to this e-mail to the Pharm/tox team for their consideration. We are

hoping to discuss this proposal with Dr. Rappaport and that he asks the Pharm/tox discipline to consider our proposal before finalizing the action letter.

Jessica, can you please forward this proposal immediately to Drs. Leshin, Wasserman and Brown? We appreciate your help on this very much. Please confirm receipt of this e-mail and let me know when we can have a meeting or t-con with Dr. Rappaport. We would appreciate having a meeting with him early Monday next week if possible due to its urgency.

This proposal is also being sent by courier today.

If you have any questions, please call me right away.

Best regards,

Mimi

From: Michelle Hershoran
Sent: Friday, July 24, 2009 1:49 PM
To: Mimi Brennan
Cc: Dan Chicoine; Brad Galer; John London; Jagat Singh
Subject: Final July 24, 2009 communication to FDA

Mimi,

Attached is the file for emailing to Jessica, which is also being sent by courier this afternoon, for receipt Monday.

We have provided 5 copies to the NDA: one archive, and four desk copies (Jessica, Paul Brown, Adam Wasserman and Steve Leschin).

Let me know if you need anything else. I am off to FedEx soon.

Thanks,
Michelle

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

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

/s/

JESSICA M BENJAMIN
10/28/2009

From: Benjamin, Jessica
To: "Mimi Brennan";
CC:
Subject: RE: PMR for NDA 20-947
Date: Wednesday, October 28, 2009 11:42:17 AM
Attachments:

Hi Mimi,

Unless technically not feasible, the Pharm Tox team would like the reproductive toxicology study timelines moved earlier in 2010. Please provide a revised set of timelines.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Monday, October 26, 2009 4:51 PM
To: Benjamin, Jessica
Subject: RE: PMR for NDA 20-947
Importance: High

Hi Jessica,

Here are the proposed timelines for the completion and submission of reports for the Fertility and Early Embryonic Development (i.e. Segment I) and Peri-and Postnatal Development (i.e. Segment III) studies in a single species with DMSO.

Segment I:

Protocol submission: May 31, 2010
Study start: July 31, 2010
Final Report submission: February 28, 2011

Segment III:

Protocol submission: May 31, 2010

Study start: July 31, 2010
Final Report submission: October 31, 2011

Jessica, please let me know if you need further information on this or if you have more questions and requests.

Thank you.

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Friday, October 23, 2009 3:58 PM
To: Mimi Brennan
Cc: Benjamin, Jessica
Subject: RE: PMR for NDA 20-947

Mimi,

Yes, this is a second PMR.

We are still working on the label at this time.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Friday, October 23, 2009 3:54 PM
To: Benjamin, Jessica
Subject: Re: PMR for NDA 20-947

Jessica,

Thanks! I'll follow up and will get back to you possibly Monday or Tuesday. Is this another request? We have not been told of this one before.

I have the timelines for the DMSO dermal carcinogenicity Study:

Study start: July 2009
Study end: July 2011
Report: August 2012

Is there anything else? When can we plan for the labeling discussion?

Regards,

Mimi

From: Benjamin, Jessica
To: Mimi Brennan
Cc: Benjamin, Jessica
Sent: Fri Oct 23 15:40:17 2009
Subject: RE: PMR for NDA 20-947
Hi Mimi,

We also need timelines for completion and submission of the following PMR study:

Completion of Fertility and Early Embryonic Development (i.e. Segment I) and Peri- and Postnatal Development (i.e. Segment III) studies in a single species with DMSO.

Please provide as soon as possible.

Regards,

Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Friday, October 23, 2009 2:42 PM
To: Benjamin, Jessica
Subject: Re: PMR for NDA 20-947

Hi Jessica,

Thank you for this good news! I'll send you the timelines asap.

Regards,

Mimi

From: Benjamin, Jessica
To: Mimi Brennan
Cc: Benjamin, Jessica
Sent: Fri Oct 23 13:37:19 2009
Subject: PMR for NDA 20-947

Hi Mimi,

Please refer to your application for Pennsaid, NDA 20-947.

The nonclinical review team has completed review of the full set of submissions regarding the lymphoma findings in the 26-week rodent toxicology study including the report of the Pathology Working Group. Upon further consideration of these additional analyses we agree the lymphoma findings in this study do not represent a signal for potential carcinogenicity of DMSO requiring pre-marketing completion of the ongoing carcinogenicity study. Therefore, consistent with the prior agreement reached between the Division and Nuvo, the rodent dermal carcinogenicity study of DMSO will be considered a Post Marketing Requirement (PMR) should the application be approved on the current review cycle. We request Nuvo provide the Division with timelines for completion and submission of the carcinogenicity study as soon as possible.

Please let me know if you have any questions.

Regards,

Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

DIMETHAID
RESEARCH INC

PENNSAID(DICLOFENAC
SODIUM)1.5% TOP LOTI

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

/s/

JESSICA M BENJAMIN
10/28/2009

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Stradley, Sara; Benjamin, Jessica;
Subject: NDA 20-947 label
Date: Tuesday, October 27, 2009 5:59:17 PM
Attachments: clean label for sponsor.doc
FDA comments for label.pdf

Hi Mimi,

I have attached a pdf version of the Pennsaid label with our changes and a clean copy with our changes accepted. Review the updated label and make any edits to the clean copy with track changes. Please note that the label has not been finalized by senior management. There are extensive changes to your proposed label. Let me know if you would like to have a brief teleconference to discuss these changes before you begin your edits. Due to the upcoming PDUFA date, we request a prompt response to this request.

Regards,
Jessica

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: REMS
Date: Friday, October 23, 2009 3:49:46 PM
Attachments: MED Guide REMS Template.doc

Hi Mimi,

The current FDAAA regulation requires all products that have a Medication Guide to have a REMS. Since Pennsaid already has the FDA-approved NSAID Medication Guide, we will need to convert it to a REMS. In order to do this, we will need a timetable for submission of assessments. The assessments need to include an evaluation of the effectiveness of the Medication Guide in communicating the risks of Pennsaid. I have attached a REMS template for you to complete. Due to the upcoming PDUFA date, we appreciate your timely response.

Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: PMR for NDA 20-947
Date: Friday, October 23, 2009 3:40:18 PM
Attachments:

Hi Mimi,

We also need timelines for completion and submission of the following PMR study:

Completion of Fertility and Early Embryonic Development (i.e. Segment I) and Peri- and Postnatal Development (i.e. Segment III) studies in a single species with DMSO.

Please provide as soon as possible.

Regards,

Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Friday, October 23, 2009 2:42 PM
To: Benjamin, Jessica
Subject: Re: PMR for NDA 20-947

Hi Jessica,

Thank you for this good news! I'll send you the timelines asap.

Regards,

Mimi

From: Benjamin, Jessica
To: Mimi Brennan
Cc: Benjamin, Jessica
Sent: Fri Oct 23 13:37:19 2009
Subject: PMR for NDA 20-947

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Please let me know if you have any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: PMR for NDA 20-947
Date: Friday, October 23, 2009 1:37:20 PM
Attachments:

Hi Mimi,

Please refer to your application for Pennsaid, NDA 20-947.

The nonclinical review team has completed review of the full set of submissions regarding the lymphoma findings in the 26-week rodent toxicology study including the report of the Pathology Working Group. Upon further consideration of these additional analyses we agree the lymphoma findings in this study do not represent a signal for potential carcinogenicity of DMSO requiring pre-marketing completion of the ongoing carcinogenicity study. Therefore, consistent with the prior agreement reached between the Division and Nuvo, the rodent dermal carcinogenicity study of DMSO will be considered a Post Marketing Requirement (PMR) should the application be approved on the current review cycle. We request Nuvo provide the Division with timelines for completion and submission of the carcinogenicity study as soon as possible.

Please let me know if you have any questions.

Regards,

Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: PMR for NDA 20-947
Date: Friday, October 23, 2009 1:37:20 PM
Attachments:

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Please let me know if you have any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: Pennsaid NDA 20-947
Date: Friday, August 07, 2009 10:14:06 AM
Attachments:

Hi Mimi,

The new PDUFA goal date is November 4, 2009. You can submit information at any time but there is no guarantee that we will be able to review it during the current review cycle. I will contact you with any additional issues that come up during the review cycle. You may submit an official meeting request to the division and we will make the decision then on a meeting. I am getting more information on question #2 below and will get back to you when I have an answer.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Wednesday, August 05, 2009 1:45 PM
To: Benjamin, Jessica
Subject: Pennsaid NDA 20-947
Importance: High

Hi Jessica,

We received the action letter extending the PDUFA date to November 4, 2009. We have a few questions that we hope you can help us with and obtain clarification from the Division as soon as possible:

1. Regarding the extended goal date, can you confirm that Nuvo will have the full 3 months available such that the information as outlined in the July 31 major amendment may be submitted and reviewed by the Division? We plan to submit most if not all information by the end of August/early September.
2. During the teleconference on July 24 with Dr. Wasserman, he informed us that another issue that has not been resolved, although a minor one, pertains to the question of label leachables. We are not sure if this is the

same question that had been asked by the CMC reviewer and that was responded to in the June 26th amendment. We need clarification of the exact issue in order for us to be able to solve and/or eliminate the problem. The CMC team during the June 19 t-con suggested that they can assist with the design of a study. Can we request for a meeting on this issue with both the P/T and CMC teams to understand and discuss possible solutions?

3. Are there any other issues other than these 2 issues raised during the June 19 t-con?
4. Can we arrange a meeting after all information have been submitted?

Jessica, it will be greatly appreciated if you can give us the answers to these questions as quickly as you can. Any of the questions that you can answer right away, please do.

Thank you so much!

Best regards,

Mimi



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020947

PDUFA GOAL DATE EXTENSION

Nuvo Research Inc.
2-1740 Lenape Road
West Chester, PA 19382

Attention: Brad Galer
U.S. Agent

Dear Dr. Galer:

Please refer to your February 4, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (diclofenac sodium topical solution) 1.5% w/w.

On August 3, 2009, we received your July 31, 2009 major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 4, 2009.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely yours,

{See appended electronic signature page}

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
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/

SARA E STRADLEY
08/04/2009

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: Pennsaid NDA 20-947
Date: Thursday, July 16, 2009 4:38:43 PM
Attachments:

Hi Mimi,

Please refer to NDA 20-947 for Pennsaid. If you decide to withdraw a facility, you will need to submit a letter requesting the facility to be withdrawn from your application. Once I receive the letter and I will forward it to the appropriate review team.

Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
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301-796-3924 *office*
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From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Thursday, July 16, 2009 4:01 PM
To: Benjamin, Jessica
Cc: Jani, Parinda
Subject: Pennsaid NDA 20-947
Importance: High

Hi Jessica,

On June 11, 2009, we submitted an amendment responding to an Information Request. One of the items was to provide contact information for the _____

_____ I discussed this with you at the time asking why the information was being asked because if a PAI inspection is planned, that we would not be using the laboratory anymore and therefore, we would withdraw this facility from the NDA as an alternate test facility for _____ testing. This same information was included in the response to the Information Request submitted on June 11, 2009.

b(4)

I was just informed that a FDA inspection for this laboratory is being requested for September 2009!

Please call me right away to discuss.

Thanks,

Mimi

From: Benjamin, Jessica
To: "Mimi Brennan";
CC:
Subject: RE: Pennsaid NDA. 20-947
Date: Tuesday, July 14, 2009 11:15:34 AM
Attachments:

Hi Mimi,

I received your voice mails and email this morning. The review is ongoing and we have no new information regarding the Pennsaid application. We will let you know as soon as we can if we have new information to relay to you.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Monday, July 13, 2009 3:19 PM
To: Benjamin, Jessica
Subject: Pennsaid NDA. 20-947
Importance: High

Hi Jessica,

I was trying to reach you on the phone earlier. Nuvo is sending the attached communications to Drs. David Jacobson-Kram and Paul Brown with copy to Dr. Rappaport and yourself today via e-mail and overnight courier for the hard copy. I was hoping that we could find out today if there has been a recommendation yet from the P/T review team.

Regards,

Mimi

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 20947 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Pennsaid Topical Solution Established/Proper Name: diclofenac sodium Dosage Form: topical		Applicant: Nuvo Research Agent for Applicant (if applicable): Brad Galer
RPM: Jessica Benjamin		Division: DAARP
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Voltaren, NDA 19-201</p> <p>Provide a brief explanation of how this product is different from the listed drug. different route of administration</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 11/3/09</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		11/4/09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None CR 12/28/06 CR - 8/7/02
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	7/8/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist³</p>	<p>yes</p>
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>8/7/02 – NA 12/28/06 – AE 11/4/09 – AP</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	<p>11/3/09 (by email)</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>2/4/09</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.
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<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	11/3/09
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	2/4/09
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	10/28/09
❖ Proprietary Name	
<ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	7/29/09
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	10/28/09
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	
❖ Internal memoranda, telecons, etc.	yes
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • PeRC (<i>indicate date of mtg; approvals only</i>) 	<input type="checkbox"/> Not applicable 7/8/09
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 6/5/00
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/4/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/9/09 and 10/29/09
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 11/3/09 (3)
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	7/9/09
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	p 55 – 8/5/02 p 21 – 12/6/06
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	10/26/09 11/4/09 <input type="checkbox"/> None 10/30/09
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/26/09

Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/25/09
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/5/09
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/2/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/2/09
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/22/09
• ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>	
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	

<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	<p>Date completed:</p> <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	<p>Date completed:</p> <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <p>Date completed:</p> <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: RE: Pennsaid NDA20-947 review
Date: Thursday, July 09, 2009 4:06:40 PM
Attachments:

Hi Mimi,

The application is still under review and the PDUFA date is August 4, 2009. I will not be able to relay any action decisions until that point.

The primary and team lead for pharm tox are Steve Leshin and Adam Wasserman. They were both on our 6/19 tcon to discuss pharm tox deficiencies. As a reminder, please direct all communications to me.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Thursday, July 09, 2009 3:55 PM
To: Benjamin, Jessica
Subject: RE: Pennsaid NDA20-947 review

Hi Jessica,

Can you tell us the time table approximately? Who are the primary and team leader for P/T ? Would that be David Jacobson-Kram and Abby Jacobs?

Thank you again Jessica for you quick response.

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Thursday, July 09, 2009 3:45 PM
To: Mimi Brennan

Subject: RE: Pennsaid NDA20-947 review

Hi Mimi,

The Pharm/Tox reviewers have not determined their final recommendation at this point.

Our primary and team leader for pharm/tox are still with us so there are no changes to the review team.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]

Sent: Thursday, July 09, 2009 2:49 PM

To: Benjamin, Jessica

Subject: Pennsaid NDA20-947 review

Hi Jessica,

I hope that you're doing well. I want to follow up on the review of our response to the Pharm/Tox and CMC issues discussed during the t-con on June 19th. Do you think we could obtain a response to our request that we be advised of the P/T team's recommendation? By the way, I have just found out that Paul Brown has left the P/T Staff. Do you know who will be reviewing from the P/T Staff?

Thanks a lot, Jessica.

Best regards,

Mimi

From: Benjamin, Jessica
To: "Mimi Brennan";
CC:
Subject: RE: Pennsaid tcon:NDA 20-947
Date: Wednesday, June 24, 2009 1:24:30 PM
Attachments:

Hi Mimi,

This calculation is not a statistical analysis or "test", it is a probability calculation.

Please provide a timeline for submission of the requested information discussed in our tcon on June 19th. It is imperative that we get the information soon in order to incorporate it into our reviews.

Thanks,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Monday, June 22, 2009 5:27 PM
To: Benjamin, Jessica
Subject: RE: Pennsaid tcon:NDA 20-947

Hi Jessica,

We have another question. Was this a one or two-tailed test?

Thanks again,

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Monday, June 22, 2009 3:01 PM
To: Mimi Brennan
Subject: RE: Pennsaid tcon:NDA 20-947

Hi Mimi,

Here is guidance provided from our statisticians:

If the rate is 3/1552 (as in the pooled controls), the probability of two or more events in 200 animals is about 0.06. If it's 2/785, the probability is about 0.03.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Monday, June 22, 2009 11:34 AM
To: Benjamin, Jessica
Subject: RE: Pennsaid tcon:NDA 20-947
Importance: High

Hi again Jessica,

We need some help. From our t-con on Friday, June 19th, Dr. Wasserman and/or Dr. Leshin talked about a statistical calculation whereby 5% was mentioned. Can we obtain the calculation or the basis of this 5%? We were not clear and are requesting for this information as quickly as possible.

Thank you very much, Jessica, for your help on this.

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Friday, June 19, 2009 4:21 PM
To: Mimi Brennan
Subject: RE: Pennsaid tcon

Hi Mimi,

As a follow-up to our teleconference today, can you forward me the names of the people on the call from Nuvo?

Thanks,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Thursday, June 18, 2009 5:56 PM
To: Benjamin, Jessica
Subject: RE: Pennsaid tcon
Importance: High

Hi Jessica,

Thank you for the names. Here are the con call numbers:

Call in number: 1-800-747-5150
Access code: 4156235

Regards,

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Thursday, June 18, 2009 5:16 PM
To: Mimi Brennan
Cc: Benjamin, Jessica
Subject: Pennsaid tcon

Hi Mimi,

The following individuals will be on the teleconference scheduled for 1:30pm tomorrow (Friday).

Dr. Adam Wasserman, Pharm/Tox Supervisor
Dr. Steve Leshin, Pharm/Tox Reviewer
Dr. Danae Christodoulou, CMC Supervisor
Dr. Olen Stephens, CMC Reviewer

Please forward a call-in number prior to the teleconference.

**Thanks,
Jessica**

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC:
Subject: RE: Pennsaid tcon:NDA 20-947
Date: Monday, June 22, 2009 3:01:17 PM
Attachments:

Hi Mimi,

Here is guidance provided from our statisticians:

If the rate is 3/1552 (as in the pooled controls), the probability of two or more events in 200 animals is about 0.06. If it's 2/785, the probability is about 0.03.

Regards,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Monday, June 22, 2009 11:34 AM
To: Benjamin, Jessica
Subject: RE: Pennsaid tcon:NDA 20-947
Importance: High

Hi again Jessica,

We need some help. From our t-con on Friday, June 19th, Dr. Wasserman and/or Dr. Leshin talked about a statistical calculation whereby 5% was mentioned. Can we obtain the calculation or the basis of this 5%? We were not clear and are requesting for this information as quickly as possible.

Thank you very much, Jessica, for your help on this.

Mimi

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To: Mimi Brennan
Subject: RE: Pennsaid tcon

Hi Mimi,

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Thanks,
Jessica

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Thursday, June 18, 2009 5:56 PM
To: Benjamin, Jessica
Subject: RE: Pennsaid tcon
Importance: High

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Thank you for the names. Here are the con call numbers:

Call in number: 1-800-747-5150
Access code: 4156235

Regards,

Mimi

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Thursday, June 18, 2009 5:16 PM
To: Mimi Brennan
Cc: Benjamin, Jessica
Subject: Pennsaid tcon

Hi Mimi,

The following individuals will be on the teleconference scheduled for 1:30pm tomorrow (Friday).

Dr. Adam Wasserman, Pharm/Tox Supervisor
Dr. Steve Leshin, Pharm/Tox Reviewer
Dr. Danae Christodoulou, CMC Supervisor
Dr. Olen Stephens, CMC Reviewer

Please forward a call-in number prior to the teleconference.

Thanks,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Michelle Hershoran":
CC: Mimi Brennan; Benjamin, Jessica:
Subject: RE: NDA 20-947 Information Request
Date: Thursday, June 04, 2009 9:04:59 AM
Attachments:

Michelle,

The answer to both of your questions below is Yes. Your analyses should extrapolate out until the specifications are exceeded and you should use 95% confidence intervals.

Let me know if you have any further questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Michelle Hershoran [mailto:mhershoran@nuvoresearch.com]
Sent: Wednesday, June 03, 2009 1:51 PM
To: Benjamin, Jessica
Cc: Mimi Brennan
Subject: RE: NDA 20-947 Information Request

Dear Jessica,

We are currently preparing the response to Question No.1, however, we have the following questions that require clarification:

- (i) Please confirm that the request for statistical analysis was to also include _____ is a potential leachable from the LDPE closure which has not been detected in our primary stability program for the HDPE Bottle/LDPE Closure (study RD-023) or in the Leachable Study (see "el report.pdf").
- (ii) Does the FDA also require the submission of the raw data from the statistical analysis in the form of a SAS transport file?

b(4)

The timeline for submission of the requested information for statistical analysis is Wednesday June 10, 2009.

Best Regards,
Michelle Hershoran
On behalf of Mimi Brennan

Michelle Hershoran
Manager, Regulatory Affairs
Nuvo Research Inc.
Tel: 905-673-6980, ext 2247

From: Michelle Hershoran
Sent: Monday, June 01, 2009 4:34 PM
To: 'Jessica.Benjamin@fda.hhs.gov'
Cc: Mimi Brennan
Subject: RE: NDA 20-947 Information Request

Dear Jessica,

This email is to provide receipt of your email information request.

Nuvo is currently reviewing the chemistry review team information request and I hope to be able to provide a timeline for submission of the requested information for question no.1 by tomorrow afternoon.

In regards to question no. 2, the requested information for the _____ testing facility is as follows:

b(4)

Contact name:

b(4)

Kind regards,
Michelle Hershoran,
On behalf of Mimi Brennan

Michelle Hershoran
Manager, Regulatory Affairs
Nuvo Research Inc.
Tel: 905-673-6980, ext 2247

From: Mimi Brennan
Sent: Monday, June 01, 2009 3:43 PM
To: Michelle Hershoran
Subject: FW: NDA 20-947 Information Request

From: Benjamin, Jessica [Jessica.Benjamin@fda.hhs.gov]
Sent: Monday, June 01, 2009 2:08 PM
To: Mimi Brennan
Cc: Benjamin, Jessica
Subject: NDA 20-947 Information Request

Hi Mimi,

Please refer to NDA 20-947 Pennsaid. See below for an information request from our chemistry review team.

1. Perform a statistical analysis as per ICH Q1A(R2) and ICH Q1E on your primary stability data for the following attributes: assay, Impurity A, — Impurity, and —
_____ Include 95% confidence intervals for your extrapolations.
2. Provide the contact person and contact information for the following purified water testing facility:

b(4)

b(4)

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 office
301-796-9713 fax

From: Benjamin, Jessica
To: "Mimi Brennan"; "Michelle Hershoran";
CC:
Subject: NDA 20-947 Information Request
Date: Wednesday, June 03, 2009 1:45:57 PM
Attachments:

Hi Mimi,

Please refer to NDA 20-947 Pennsaid. See below for an information request from our pharm tox review team.

1. In the 6-month repeated dosing toxicology study of DMSO applied topically to rats (Study RD-1000-07-05, conducted at _____ in 2007-2008), there were incidences of lymphoma in rats less than 10 months of age. What is the historical incidence of lymphoma in this age and strain of animals in studies of comparable duration at this facility?

b(4)

2. In the 3-month repeated dosing toxicological study of DMSO applied topically to rats (Study AB20TB,7D31.BTL, conducted at _____ in 2005 to 2006), there were incidences of nephroblastoma in rats less than 6 months of age. What is the historical incidence of nephroblastoma in this age and strain of animals in studies of comparable duration at this facility?

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products

Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: NDA 20-947 Information Request
Date: Monday, June 01, 2009 2:08:26 PM
Attachments:

Hi Mimi,

Please refer to NDA 20-947 Pennsaid. See below for an information request from our chemistry review team.

1. Perform a statistical analysis as per ICH Q1A(R2) and ICH Q1E on your primary stability data for the following attributes: assay, Impurity A, _____ Impurity, and _____ Include 95% confidence intervals for your extrapolations.

b(4)

2. Provide the contact person and contact information for the following _____ testing facility:

b(4)

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: NDA 20-947 request
Date: Tuesday, May 26, 2009 10:49:03 AM
Attachments:

Hi Mimi,

Please refer to NDA 20-947 for Pennsaid. We are requesting samples of the bottle and dropper for Pennsaid. You can send the package directly to my office at the address below. Let me know if you have any questions.

Regards,
Jessica

*Mailing address: Jessica Benjamin
Food and Drug Administration
10903 New Hampshire Avenue
W01-3191
Silver Spring, MD 20993-0002*

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

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

/s/

JESSICA M BENJAMIN
10/28/2009

From: Benjamin, Jessica
To: "Mimi Brennan";
CC: Benjamin, Jessica;
Subject: NDA 20-947 Information Request
Date: Tuesday, March 31, 2009 1:08:46 PM
Attachments:

Hi Mimi,

Please refer to NDA 20-947 for Pennsaid. After initial review of your application, we have the following chemistry-related questions:

1. You have calculated an AET with the assumption that only — of leachable material will be absorbed by the skin based on the absorption of the drug substance. Impurities may absorb into the skin to a different extent; therefore, to it must be assumed that 100% of leached material will be absorbed. Re-evaluate your leachable data with an AET of ———— This AET was calculated by dividing the qualification threshold by the daily dose: —————

b(4)

2. The ratio of drug product volume to container closure components (HDPE bottle, LDPE closure, and label) will vary for the 15 mL, 60 mL, and 150 mL configurations. Calculate Total Daily Exposures and ADI/TDE for the 15 mL and 150 mL configurations (similar to Table 4 in the extractable/leachable study) with the assumption that potential leachables will scale linearly from the 60 mL configuration according to amount of each packaging component.

3. Provide a proposed *in-use* shelf life along with data and justification to support this specification. The *in-use* shelf life should account for the expected use of the product which will expose the drug product to oxidative conditions, which may affect the stability of the drug product.

4. Provide more specific information concerning the "slight smudging of label text was observed for 4 lots (few bottles of each lot) stored in the horizontal position (T3). The smudging of label text was caused due to a minor leakage of

the product in the horizontal position. The problem was more evident in the bottles of the small fill size (3 lots of the 15 ml and 1 lot of the 60 mL). The legibility of the label text is also not impaired due to this discoloration.”

- a. Was the smudging caused by leaks from a single bottle or from each bottle that had smudging?
- b. What volume of drug product was lost to cause this smudging?
- c. What does the applicant propose to control this drug product leakage?
- d. Is this leakage inherent in the container closure configuration?

Thank you for your prompt attention to these requests. Feel free to contact me with any questions or concerns.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "mbrennan@nuvoresearch.com";
CC:
Subject: NDA 20-947; Pennsaid
Date: Wednesday, February 18, 2009 5:12:02 PM
Attachments: NDA 20-947 Ack ltr.pdf

Hi Mimi,

Thank you for your voice mail and introduction today. To follow up on your question, we have accepted your complete response for review. It has been granted a 6 month clock, with an PDUFA date of August 5, 2009. I have attached the letter that was signed yesterday and sent to your authorized US agent. In the future, I will contact you if we need any additional information for our review. With my current work load, I will not be able to respond to multiple, daily phone calls but will make every effort to answer your questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 office
301-796-9713 fax



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-947

Nuvo Research Inc.
2-1740 Lenape Road
West Chester, PA 19382

Attention: Brad Galer
U.S. Agent

Dear Dr. Galer:

We acknowledge receipt on February 5, 2009, of your February 4, 2009 resubmission to your new drug application for PENNSAID Topical Solution (diclofenac sodium topical solution) 1.5% w/w.

We consider this a complete, class 2 response to our December 28, 2006 action letter. Therefore, the user fee goal date is August 5, 2009.

If you have any questions, call me at (301)796-3924.

Sincerely,

{See appended electronic signature page}

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
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/

Jessica Benjamin
2/17/2009 01:29:01 PM



NDA 020-947

New Drug Application

PENNSAID[®] Topical Solution
(diclofenac sodium topical solution) 1.5% w/w

RE: THE ATTACHED "SMALL BUSINESS WAIVER"

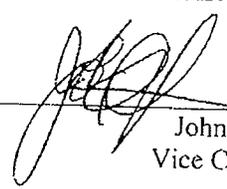
Nuvo Research Inc. hereby certifies the attached "Small Business Waiver" issued on February 3, 1998 to Dimethaid Research Inc. (name changed to Nuvo Research Inc, effective September 30, 2005), is applicable to the NDA 20-947 resubmission, which is being submitted as a complete response to the FDA approval letter issued December 28, 2006.

The conditions stated in the attached "Small Business Waiver" (i.e. "Dimethaid employs fewer than 500 persons & "according to FDA records, NDA 20-947 is the first NDA submitted for review") still apply, qualifying Nuvo Research Inc. as a small company.

Dated, this 28 day of January, 2009.

NUVO RESEARCH INC.

Per: _____


John London
Vice Chairman

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

This completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Dimethaid International Inc.
(a fully-owned subsidiary of Nuvo Research Inc.)
Los Abedules, Appleby Gardens St. James, Barbados

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 020-947

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
 YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(246) 432-5849

3. PRODUCT NAME

PENNSAID® Topical Solution (1.5% w/w diclofenac sodium)

6. USER FEE I.D. NUMBER

3373

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director, Regulatory Affairs & Clinical
research

DATE

June 23, 2006



NDA 020-947

New Drug Application

PENNSAID[®] Topical Solution
(1.5% w/w diclofenac sodium)

RE: THE ATTACHED "SMALL BUSINESS WAIVER"

Nuvo Research Inc., the parent company of Dimethaid International Inc., hereby certifies the attached "Small Business Waiver" issued on February 3, 1998 to Dimethaid Research Inc. (name changed to Nuvo Research Inc, effective September 30, 2005), is applicable to the NDA 20-947 resubmission, which is being submitted as a complete response to the FDA non-approval letter issued August 7, 2002.

The conditions stated in the attached "Small Business Waiver" (i.e. "Dimethaid employs fewer than 500 persons & "according to FDA records, NDA 20-947 is the first NDA submitted for review"), still apply qualifying Nuvo Research Inc. as a small company.

Dated, this rd 23 day of JUNE, 2006.

NUVO RESEARCH INC.

Per: 
Daniel Chicoine
Chairman

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Dimethaid International Inc.
Los Abedules, Appleby Gardens
St. James, Barbados

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
20-947

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA.)

2. TELEPHONE NUMBER (Include Area Code)

(246) 432-5849

3. PRODUCT NAME

PENNSAID Topical Solution

6. USER FEE I.D. NUMBER

3373

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director

DATE

August 7, 2001

Printed by Sandra Cook
Electronic Mail Message

Date: 08-Jan-1998 03:10pm
From: RCV_MUIR
RCV_MUIR@DFM42@MRGATE@FDACD
Dept:
Tel No:

Subject: USER FEE PAYMENT & ARREARS LIST

NOTE: * denotes entries since last report

APPLICATION PAYMENTS

The following application payments have been received:

Date	Firm	Userfee ID	Application #	Payment
------	------	------------	---------------	---------

* 08-JAN-98	DIMETHAID RESEARCH I	3373	N020947	102,500
07-JAN-98				
06-JAN-98				
06-JAN-98				
06-JAN-98				
02-JAN-98				
30-DEC-97				
30-DEC-97				
30-DEC-97				
23-DEC-97				
19-DEC-97				
19-DEC-97				
18-DEC-97				
17-DEC-97				
17-DEC-97				
15-DEC-97				
15-DEC-97				
09-DEC-97				
09-DEC-97				
08-DEC-97				

b(4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Office of the Chief Mediator and Ombudsman
Food and Drug Administration
5600 Fishers Lane
Room 14-105, HF-7
Rockville, MD 20857

February 3, 1998

Rebecca E. Keeler
President and CEO
Dimethaid Research Inc.
1405 Denison Street
Markham, Ontario L3R 5V2

Re: Prescription Drug User Fee Act
Small Business Waiver Request
Our file: 98.005

Dear Ms. Keeler:

This responds to your October 14, 1997 letter on behalf of Dimethaid Research Inc. (Dimethaid) requesting that the Food and Drug Administration (FDA) waive payment of the application fee assessable upon submission of the marketing application for PENNSAID™ Topical Lotion, NDA 20-947, as prescribed by the small business waiver provision of the Prescription Drug User Fee Act reauthorization contained in the Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 379h(d)(1)(E). FDA hereby grants a waiver of payment of the application fee for reasons stated below.

The small business waiver provision entitles a qualified small business to a waiver of 100 percent of the application fee when the business meets two criteria: first, a business must employ fewer than 500 persons, including employees of affiliates; and second, the marketing application must be the first human drug application that a company or its affiliate submits to FDA for review, 21 U.S.C. § 379h(d)(3).

FDA's decision to grant a small business waiver to Dimethaid is based on two findings. First, by letter dated January 9, 1998, the Small Business Administration (SBA) determined that Dimethaid employs fewer than 500 persons, including employees of its affiliates: Akorn Pharmaceutical Canada

Dimethaid Research, Inc.
February 3, 1998
Page 2

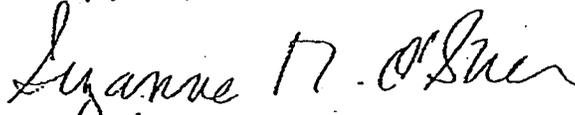
Ltd., Femina Inc., Excelpharm Inc., Dimethaid Management Inc., Dimethaid Operations Inc., Dimethaid Immunology Inc., Dimethaid International Inc., and Oxo Chemie AG. Second, according to FDA records, NDA 20-947 is the first human drug application submitted for review by Dimethaid or its affiliates. Therefore, FDA grants Dimethaid a waiver of payment of 100 percent of the FY 1998 application fee covering PENNSAID™ Topical Lotion, NDA 20-947.

FDA's Office of Financial Management has been notified of this waiver and will refund the \$102,500 (FY 1997 application fee) that Dimethaid paid to FDA on January 8, 1998 for NDA 20-947 in partial payment of the FY 1998 application fee of \$258,846. If no refund is received by February 18, 1998 contact Mr. Michael Roosevelt, Chief, Systems Accounting Branch, at 301-827-5088.

Please note that as announced in User Fee Correspondence 3, dated August 5, 1993, FDA plans to disclose information about its actions granting or denying waivers, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this waiver, please contact Kathleen Locke, of this office, at 301-827-3390.

Sincerely yours,



Suzanne M. O'Shea
Deputy User Fee Waiver Officer

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Dimethaid International Inc. Los Abedules, Appleby Gardens St. James, Barbados	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 20-947
2. TELEPHONE NUMBER (Include Area Code) (246) 432-5849	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME PENNSAID Topical Solution	6. USER FEE I.D. NUMBER 3373

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director	DATE August 7, 2001
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Record of Telephone Conversations

Date of Report: 26 May, 1999 ; Date of Contact: 25 May, 1999

By: George E. Markus Contact: Mike Jones, CSO

Incoming or Outgoing: Incoming Company/Organization: FDA, CDER,

Phone Number: (301) 594-5624

Regarding: Waiver for NDA 20-947

M. Jones responded to our request for clarification of the waiver requirements for the Pennsaid™ NDA submission (re-opening of the application). The following was stated:

- Same rule applies for waivers as for companies who have paid submission fees (i.e. If a company paid fees, the re-opening of the application does NOT require new payments. Similarly, if a waiver was applicable at the time of the initial submission, the re-opening of the application does NOT require a new waiver.)
- Based on the above, the original waiver covers the re-opening of our NDA file. Dimethaid can include a copy of the original waiver at the time the application is submitted / re-opened. Dimethaid to also reference this telephone contact report in our submission for administrative purposes.

Duration of conversation: Approx. 10 minutes

cc: R. E. Keeler
K. Williams
File

J:\PROJECTS\PENNSAID\REG-AFF\CORRESP\EXTERNAL\FDA\waiver-25may99.doc



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-947

Dimethaid International, Inc
c/o Nuvo Research, Inc.
2220 Chalkwell Drive
Midlothian VA 23113-3884

Attention: Mimi D. Brennan
Director, Clinical Research and Regulatory Affairs

Dear Ms. Brennan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PENNSAID (diclofenac sodium) Topical Solution.

We also refer to the teleconference between representatives of your firm and the FDA on June 4, 2007. The purpose of the meeting was to discuss the designation of special case active. You submitted a correspondence dated April 20, 2007 in support of your position.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1298.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 4, 2007
TIME: 4:30 PM EST
LOCATION: Teleconference
APPLICATION: NDA 20-947/IND 42,773
DRUG NAME: PENNSAID (diclofenac sodium)
TYPE OF MEETING: Guidance
MEETING CHAIR: Bob Rappaport, MD, Director, Division of Anesthesia, Analgesia and Rheumatology Products
MEETING RECORDER: Sara Stradley, Chief, Project Management Staff
FDA ATTENDEES:

Bob Rappaport, MD Division Director
Rigoberto Roca, MD, Deputy Division Director
Sara Stradley, Chief, Project Management Staff

EXTERNAL CONSTITUENT ATTENDEES:

Dan Chicoine, Nuvo Research, Chairman
Consultant

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Background:

The purpose of the meeting was to discuss the designation of special case active of DMSO.

Discussion:

Dr. Rappaport stated that there are still ongoing internal discussions regarding penetration enhancers and the special case active/inactive ingredient categorization. Dr. Rappaport noted, however, that the terminology will not have an impact on the requirement for an adequate safety evaluation of DMSO.

Dr. Rappaport stated that the Sponsor will need to evaluate DMSO in two species (by the dermal route) and will need full systemic histopathology. It was noted that, during previous review cycles, the Sponsor was not told of the need for a dermal carcinogenicity assessment. However, the dermal carcinogenicity study should be initiated now. If the dermal toxicity studies do not show any signals, the dermal carcinogenicity study can be continued post-approval.

Please refer to Attachment 1 below for a post teleconference email exchange.

ATTACHMENT 1

The following is an email exchange (in chronological order) that provided clarification to the discussion that occurred during the teleconference.

-----Original Message-----

From: Stradley, Sara [mailto:sara.stradley@fda.hhs.gov]
Sent: Tuesday, June 05, 2007 3:18 PM
To: Mimi Brennan
Cc: Stradley, Sara
Subject: follow-up to TC on June 4, 2007 (pennsaid)

Mimi

As a follow-up to the telecon on June 4, 2007.

You will need to evaluate DMSO in two species (the minipig [12-month study] and a rodent [6-month study]) by the dermal route and you will need full systemic histopathology. The 12-month study instead of 9 months is due to information from a recent ICH meeting in which data was shown that some eye changes (cataracts, lens changes, etc) occurred at 12 months that was not picked up at 9 months.

As a clarification, you should initiate your dermal carcinogenicity study now. However, if the dermal toxicology studies do not show any signals, you can continue the dermal carcinogenicity study post-approval.

Let me know if you have any further questions. Thanks

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
email: Sara.Stradley@fda.hhs.gov

From: Mimi Brennan [mailto:mbrennan@nuvovresearch.com]
Sent: Wednesday, June 06, 2007 12:13 PM
To: Stradley, Sara
Subject: RE: follow-up to TC on June 4, 2007 (pennsaid)

Sara,

Thank you much for the immediate response and clarification. Are we going to get an official minutes of the TC? Sorry, but we have one more thing to clarify with Dr. Mellon regarding the dermal carcinogenicity study that we will be starting. Can we do this study in rats, being that we have already the 3-month study that would serve as a dose range finding study?

Thanks again, Sara!

Regards,
Mimi

-----Original Message-----

From: Stradley, Sara [mailto:sara.stradley@fda.hhs.gov]
Sent: Friday, June 08, 2007 10:42 AM
To: Mimi Brennan
Subject: RE: follow-up to TC on June 4, 2007 (pennsaid)

Mimi-
The rat is acceptable.

Sara

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Friday, June 08, 2007 12:02 PM
To: Stradley, Sara
Subject: RE: follow-up to TC on June 4, 2007 (pennsaid)
Importance: High

Sara,

Thank you for the quick response once again. Short of the official meeting minutes which will be soon forthcoming, can you please confirm our understanding of the following points from the June 4th teleconference since I was not present at the meeting ?

1. Nuvo needs to evaluate DMSO in two species (12-month minipig study and a rodent 6-month study via the dermal route). Full systemic histopathology is required.
2. A dermal carcinogenicity study should be initiated now. The rat is acceptable.
3. If the dermal tox studies do not show any signals, the dermal carcinogenicity study can continue post approval.

Does this mean that 1 dermal carc study is acceptable?

This assumes also that Nuvo shall have a biobridge to Solaraze or a right of reference?

Sara, is it possible to receive the official minutes in less than 30 days? Can we rely on the e-mails for confirmation in order for us to move forward which would include discussions of these studies with our employees, vendors, consultants and therefore publicly since we are a very small public company?

We will appreciate your earliest response.

Thank you for your patience and continuing assistance, Sara. Have a nice weekend.!

Mimi

From: Stradley, Sara
Sent: Friday, June 08, 2007 12:32 PM
To: 'Mimi Brennan'
Cc: Stradley, Sara
Subject: RE: follow-up to TC on June 4, 2007 (pennsaid)

Mimi-

You will need to evaluate DMSO in two species (the minipig [12- month study] and a rodent [6-month study]) by the dermal route and you will need full systemic histopathology. The 12 month study instead of 9 months is due to information from a recent ICH meeting in which data was shown that some eye changes (cataracts, lens changes, etc) occurred at 12 months that was not picked up at 9 months. You should initiate your dermal carcinogenicity study now (rat species is acceptable). However, if the dermal tox studies do not show any signals, you can continue the dermal carcinogenicity study post-approval.

Please submit your carcinogenicity protocol for concurrence by the eCAC prior to initiation. You should review the following ICH guidance documents:

S1B Testing for Carcinogenicity of Pharmaceuticals	Final 2/28/1998
S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals	Final 3/1995
S1C(R) Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes	Final 12/4/1997

as well as the following FDA Guidance document:

Carcinogenicity Study Protocol Submissions	Final 5/22/2002
--	-----------------

that are available on the following web page: <http://www.fda.gov/cder/guidance/index.htm>

I have no comment on the biobridge study since this was not discussed during the telecon. The meeting minutes will be issued within 30 days of the telecon. I cannot guarantee that I will have the minutes any earlier. These emails capture the main points of the discussion that occurred during the telecon.

I cannot comment on how/what you discuss with your employees/contractors.

Sara

-END-

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

/s/

Sara Stradley
7/20/2007 08:36:39 AM



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 New Drug Application (NDA) submitted under section 505(i)/505(b) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (diclofenac sodium topical solution) 1.5% w/w.

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2007. The purpose of the meeting was to discuss your plans to address the deficiencies in the December 28, 2006 approvable letter. Your questions are in *italics* and the Division's responses are in **bold**.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc: Mimi D. Brennan, Nuvo Research, Inc.

Memorandum of the Minutes

MEETING DATE: Tuesday, January 30, 2007

TIME: 10:00 a.m. - 11:00 a.m. (EST)

LOCATION: FDA, White Oak, Conference Rm #1309,
10903 New Hampshire Ave, Silver Spring, MD 20993-0002

APPLICATION: NDA 20-947 PENNSAID® Topical Solution (diclofenac sodium
topical solution) 1.5% w/w

INDICATION: Topical treatment for relief of the signs and symptoms of OA of
the knee(s)

SPONSOR: Dimethaid International, Inc. (c^o Nuvo Research, Inc.)

TYPE OF MEETING: End of Review Conference (21 CFR 314.102(d))

MEETING CHAIR: Jeff Siegel, M.D.

MEETING RECORDER: Paul Z. Balcer

FDA Attendees

Name	Title
Bob A. Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Rigoberto Roca, M.D.	Deputy Director (Rheumatology Team)
Jeff Siegel, M.D.	Medical Team Co-Leader (Rheumatology Team)
Larissa Lapteva, M.D.	Clinical Reviewer
Dan Mellon, Ph.D.	Pharmacology and Toxicology Supervisor, DAARP
Lawrence S. Leshin, D.V.M., Ph.D.	Pharmacology and Toxicology Reviewer
Rik Lostritto, Ph.D.	Director, Division of Pre-Marketing Assessment III & Manufacturing Science (DPAMS)/ONDQA
Ravi Harapanhalli, Ph.D.	Branch Chief, DPAMS
Ali Al-Hakim, Ph.D.	Chemistry Reviewer – PAL
Sue-Ching Lin, M.S., R.Ph.	Chemistry Reviewer
Paul Z. Balcer	Regulatory Health Project Manager
Shanna Oldewurkel	Pharm.D. Candidate, Pharm. D. Student Program

Dimethaid International, Inc./Nuvo Research, Inc. Attendees

Name	Title
Henrich Guntermann, M.D.	President, CEO
Daniel Chicoine	Chairman
Zev Shainhouse, M.D.	Medical Director
Jagat Singh, Ph.D.	Director, Research and Development
Mimi D. Brennan	Director, Regulatory Affairs & Clinical Research
Michelle Hershoran	Manager, Global Regulatory Affairs

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The Sponsor's questions are in *italics*, Division's responses are in **bold** and discussion in normal font. The Division responses were provided to the Sponsor on Monday, January 29, 2007.

After brief introductions, the Sponsor thanked the Division for providing the comments in advance of today's meeting and reiterated its commitment to safety of this drug since filing the original NDA in 2001. The Sponsor presented the Division with the specific agenda items for discussion and information on how Nuvo Research, Inc. can proceed with the application. The Sponsor's questions and the Division's responses were then addressed.

Introductory statement from FDA:

Although we generally seek to identify all deficiencies during the initial review period, we sometimes become aware of deficiencies only during a subsequent review period. It would be inconsistent with section 505(d) of the FFDCA and FDA regulations to approve an application despite an applicant's failure to address deficiencies solely because those deficiencies were identified only after issuance of a complete response letter.

Your product contains a novel excipient, as described in the following guidance document: *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005)* which is available at <http://www.fda.gov/cder/guidance/guidance.htm>.

"the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration.*" (Emphasis added).

DMSO is a novel excipient in that it is not contained in any FDA approved drug product intended for the dermal route of administration on intact skin. The referenced data regarding the safety of DMSO is not from GLP studies nor did you submit the raw data from these studies for review. Prior to approval of a drug product with DMSO via this route of administration and with these relatively high concentrations, sufficient characterization of the safety of DMSO for use as an excipient via this route and in this concentration should be provided. Once that is provided, DMSO can be listed in the Inactive Ingredient's Guide and determined that it is safe for use chronically by other drug product manufacturers. The Agency is obligated to base such a determination on adequate nonclinical safety data. Although the existing clinical data to date are supportive, they alone cannot establish safety and therefore data from sufficient chronic dermal nonclinical studies with complete histopathological evaluations should be provided (either by reference to acceptable literature or by newly conducted studies).

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.*

Dimethaid's Response & Question:

The amount of DMSO applied to the knee is unlikely to result in excess exposure to toxins or microbiological agents. There are many topical products (which may involve whole body exposure) and patches that use solvents and/or penetration enhancers, and they do not appear to have caused such exposures. We believe that it is reasonable to add labeling information to further ensure the safe use of our product. In the event of deliberate application of another product over the entire knee after using PENNSAID®, its potential interaction with PENNSAID® would be controlled by waiting for the PENNSAID® (DMSO) to disappear from the surface of the skin by evaporation and penetration into the epidermis. Clinical experience in 11 of the controlled clinical trials (Phase I to III) over the last 13 years has demonstrated that this time interval is approximately twenty minutes. To be conservative, Dimethaid proposes that the label, under WARNINGS, _____

_____ The proposed labeling specifically and fully addresses this issue newly raised by the Division in the December 28, 2006 Approvable Letter, that the DMSO component of the product could possibly result in absorption of toxins and microbiological agents. Since the stratum corneum is the site of the percutaneous barrier to such chemicals, the potential for DMSO in PENNSAID® to dissolve, and facilitate the percutaneous penetration of a chemical requires direct contact on the outermost surface of the skin between that chemical and DMSO. How much of the chemical will dissolve depends on the amount of DMSO on the surface of the skin. A single 1.2 mL dose of PENNSAID® will contain approximately 0.6 mL of DMSO which will be spread evenly over a knee with surface area approximately 800 cm², resulting in 0.0008 mL of DMSO per cm². DMSO rapidly

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penetrates through the stratum corneum within 5 minutes (Kolb et al. 1967). Once the application site surface is dry, there can be no facilitation of absorption by DMSO, since Fick's law describes that only substances in solution participate in the concentration gradient which provides the energy to drive penetration across the stratum corneum barrier.

Additionally, DMSO does not universally dissolve all environmental chemicals of toxicological interest. The June 13, 2006, Board Meeting of the National Toxicology Program Board of Scientific Counselors stated: "... other solvents should be investigated because many environmental substances are relatively insoluble in DMSO" (http://ntp.niehs.nih.gov/files/BSC_Minutes_Final%5B2%5D.pdf).

Therefore, the finding that the DMSO, following topical application of PENNSAID[®], will rapidly penetrate and not persist beyond 20 minutes on the stratum corneum (where it must be to permit increased absorption of likely toxins) is a sufficient basis for the proposed labeling, as described above.

Does the Agency agree with this approach?

FDA's Response:

Your proposal to address the concern regarding the potential enhanced absorption of environmental toxins via labeling can be considered for acceptability, if the proposed advice is supported by actual data. However, you have not provided data to support your claim that the use of topical DMSO as indicated in this drug product does not result in excess exposure to toxins or microbiological agents.

Reference to information on other penetration enhancers does not provide relevant information to support the safety of your drug product formulation. The Agency's concerns that should be addressed pertain to only the penetration enhancer you have included in your drug product.

Data from multiple applications of the drug product are also necessary to characterize the chronic effects of DMSO on the skin, since DMSO can solubilize the fat and proteins that comprise the skin itself, thereby leading to persistent and perhaps permanent changes in the skin integrity.

You should conduct nonclinical studies in a mini-pig model to obtain the data to support your assertion that after both single and multiple dose application of Pennsaid, applying a substance (skin moisturizers, sunscreens, insect repellent) to the same site does not result in absorption of the substance into the skin. You should study a range of toxicants for absorption locally applied with the Pennsaid formulation as used in people. Address question of size of compounds, hydrophilic-lipophilic range, and systemic levels and dermal levels as well as toxic reaction, therefore use negative and known positive controls. Although 20 minutes may be an appropriate time for drying to occur based your of clinical experience, you have not submitted data to demonstrate that after a 20 minute waiting time, the permeability of the skin is no longer altered and that subsequent exposure to environmental toxins is no longer enhanced.

Discussion:

The Sponsor questioned the use of the nonclinical studies in a mini-pig model to address the concerns of the Division, i.e. data to support the Sponsor's assertion that after both single and multiple dose application of PENNSAID, that subsequent application of a substance (skin moisturizers, sunscreens, insect repellent) to the same site does not result in absorption of the substance into the skin. The Sponsor wanted to know specifics as to the information to track, i.e. compound size, hydrophilic/hydrophobic solubility, systemic and dermal levels of DMSO, toxic reaction monitoring, and the number of animals to be studied, and how these findings would be translated into the future labeling of PENNSAID.

The Division explained that in the originally proposed PENNSAID label, a drying period of 20 minutes was proposed. Further discussion at that time indicated that after the skin is dry, other substances would not be absorbed through the skin. The Division explained that at present there are no data to indicate whether substance are or are not absorbed after the site of application is dry or what happens if the area of the application gets wet. The Division does not have data indicating where the DMSO resides (depot effect) after PENNSAID is applied (under the skin) or if is completely absorbed. The Division did not present specific experimental designs and parameters to be studied, but noted that the Sponsor should propose a means to best address our concerns. The Division asked the Sponsor to provide a protocol design to substantiate that after 20 minutes of applying PENNSAID the permeability of the skin is no longer altered and that subsequent exposure to environmental toxins is no longer enhanced. The Sponsor noted their intention to submit a proposal for a human clinical pharmacokinetic study using sunscreen to observe for any penetration interaction with PENNSAID.

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 excipients due to its high concentration.*

Dimethaid's Response & Question:

The need to assess the toxicological potential of PENNSAID® in repeat-dose dermal toxicology studies was not addressed in the August 7, 2002 NA letter. Therefore the Sponsor that there were no outstanding issues regarding NonClinical Pharmacology and Toxicology. There can be utility in conducting such repeat dose dermal toxicity studies prior to pivotal studies in human subjects, especially in the setting of products containing a new molecular entity (which PENNSAID® does not contain). However, there are now substantial clinical data on the safety of this product in the most relevant species, human, which greatly reduces the utility in conducting chronic repeat-dose toxicity studies in animals at this point in the development program. Over 6425 people have been exposed to our product in clinical trials, including 911 patients treated in seven Phase 3 controlled trials of up to 12 weeks duration, and 793 patients treated in an open label study (463 patients treated for at least 6 months,

and 114 patients treated for at least 12 months) (see ISS, Table 2). In addition, PENNSAID® has been marketed in Canada (since May 2003), United Kingdom (since March 2001), Italy (since May 2003) and Portugal (since 2004). The topical effects of PENNSAID® have been evaluated in humans, including a full human dermal safety battery, and unlike other organ systems, the skin can be immediately evaluated everyday. Additionally, diclofenac has been fully evaluated for toxicity and carcinogenicity in innovator products already approved by the Agency. All of the excipients in our product are listed in the FDA's Inactive Ingredients guide. A brief summary of the type of products that include PENNSAID® are listed Table 2 of the briefing package.

Table 2: Brief Summary of FDA's Inactive Ingredients Database

Excipient	Route of Administration	Concentration
Dimethyl sulfoxide	IV	Not provided
	Subcutaneous; implant Topical; dressing	104 mg 16.5 mg
Propylene glycol	IM, IV	40%
	Oral	Up to 92%
	Dermal	Up to 98%
Alcohol	IV	49%
	Oral	Up to 94.7%
	Dermal	Up to 91%
Glycerin	IM, IV, SC	16%
	Oral	Up to 79%
	Dermal	Up to 50%

Source: Appendix 9.1 - Summary of FDA Inactive Ingredient Database for Approved Drug Products—Propylene glycol, glycerin and alcohol

A single 1.2 mL dose of PENNSAID® will contain approximately — of each propylene glycol, glycerin and alcohol. Even if the entire applied dose of each excipient in PENNSAID® could penetrate the skin and then enter the systemic circulation, each would present a dermal and systemic exposure level that is lower than that of widely used, chronic treatment, dermal and oral prescription and over-the-counter medications approved by the FDA (see Table 3).

b(4)

Table 3: Brief Summary of FDA's Approved Drug Products

Inactive Ingredient	Oral	Topical
DMSO		Viadur (leuprolide acetate implant); Dermagraft; RIMSO-50® (interstitial cystitis)

Propylene glycol	Acetaminophen and Codeine Phosphate Solution; Agenerase (amprenavir) oral solution; Celexa (Citalopram) Oral Solution; Claritin Syrup; Imodium A-D (loperamide) Liquid; Neoral Oral Solution (cyclosporine oral solution, USP); Zyrtec Syrup (cetirizine HCl); Kaletra Oral Solution (lopinavir/ritonavir)	Elcon (mometasone furate) Lotion 0.1%; Lac-Hydrin Cream (Ammonium Lactate); Lidoderm (lidocaine patch 5%); Luxiq (betamethasone valerate) Foam; Retin-A Micro (tretinoin gel) microsphere; Rogaine For Men Extra Strength (minoxidil): 50% propylene glycol Testim 1% (testosterone gel); Vivelle (estradiol transdermal system); Xolegel (Ketoconazole, USP) Gel 2%
Glycerin	Acetaminophen and Codeine Phosphate Solution; Claritin Syrup; Imodium A-D (loperamide) Liquid; Zoloft (sertraline) Oral Concentrate; Zyrtec Syrup (cetirizine HCl); Infants Motrin (ibuprofen); Kaletra Oral Solution (lopinavir/ritonavir)	Androderm Testosterone Transdermal System; Lac-Hydrin Cream (Ammonium Lactate); Lidoderm (lidocaine patch 5%); Retin-A Micro (tretinoin gel) microsphere; Testim 1% (testosterone gel); Xolegel (Ketoconazole, USP) Gel 2%
Alcohol	Acetaminophen and Codeine Phosphate Solution; Zoloft (sertraline) Oral Concentrate: 12%; Zantac (ranitidine) Syrup: 7.5%; Kaletra Oral Solution (lopinavir/ritonavir): 42.4%	Androderm Testosterone Transdermal System; Androgel (1% testosterone gel): 67%; Luxiq (betamethasone valerate) Foam: 60.4%; Rogaine For Men Extra Strength: 30% alcohol Testim 1% (testosterone gel): 74%

The Sponsor contends, therefore, that the potential level of absorption of the product components in PENNSAID® does not pose an unknown safety risk from potential exposure. Even if complete absorption results in maximum dermal and systemic exposure, which is highly unlikely (for example, only 6% of the diclofenac is absorbed from PENNSAID® containing DMSO), then these exposures to the inactive ingredients in PENNSAID® are still lower than that obtained from many marketed chronic use topical and oral products. Moreover, diclofenac has been fully evaluated for toxicity and carcinogenicity in products approved by the Agency and currently marketed. Thus, the available information indicates that there is not sufficient additional utility to be derived from repeat-dose dermal toxicity animal testing with PENNSAID®

Does the Agency agree with this assessment?

FDA's Response:

The Agency does not agree that you have provided adequate data to support the safety of the drug product formulation. Your product contains a novel excipient, as described in the following guidance document: *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005)* which is available at the following location: <http://www.fda.gov/cder/guidance/guidance.htm>.

“the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration.*” (Emphasis added).

DMSO in your drug product is a novel excipient, since it has not previously been used via the dermal route of administration on intact skin for any FDA approved drug product. The reference drug products listed in your table 3 do not provide adequate exposure or experience for either the route of administration, dose of DMSO used, and/or duration of indication.

For treatment of one knee, 550 mg of DMSO per single application or 2200 mg of DMSO per day constitutes amounts far in excess of the inactive ingredient database presented in your table 2. Your rationale for the safety of exposure to the other components of this drug product may be adequate based on the previous exposure to comparable levels via the IV route of administration (which would be the worst case scenario for your drug product containing DMSO) and if the approved use of the compound is for a chronic indication.

If you provide adequate nonclinical data to demonstrate the safety for the maximum daily exposure to these excipients for a chronic condition, the requested repeat-dose dermal toxicology study may be conducted with only the novel excipients, DMSO.

The referenced data regarding the safety of DMSO is not from GLP studies nor did you submit the raw data from these studies for review. Prior to approval of a drug product with DMSO via this route of administration and with these relatively high concentrations, sufficient characterization of the safety of DMSO for use as an excipient via this route and in this concentration should be provided. Once that is provided, DMSO can be listed in the Inactive Ingredient's Guide and determined that it is safe for use chronically by other drug product manufacturers.. The Agency is obligated to base such a determination on adequate nonclinical safety data. Although the existing clinical data to date are supportive, they alone cannot establish safety and therefore data from sufficient chronic dermal nonclinical studies with complete histopathological evaluations should be provided (either by reference to acceptable literature or by newly conducted studies).

Discussion:

The Sponsor informed the FDA that it has completed a 90-day repeat-dose dermal toxicity rat study with DMSO, with systemic exposure that reached 60 times human exposure. The Division responded that, for products intended for chronic exposure, longer studies are required to demonstrate safety. The Sponsor noted their intention to submit the final study report for the 90-day toxicology study to the IND as well as other chronic dermal toxicity studies on DMSO in published literature.

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

b(4)

Dimethaid Question:

Dimethaid requests clarification on how the total daily intake limit and the corresponding acceptance criterion outlined in the AE letter were determined for the identified _____ impurity, _____ Although the August 7, 2002, NA letter did not contain any reference to this impurity, either as a request for additional information or as a notification that it represented a structural alert which would require qualification if found in the drug product at a limit of _____ the Sponsor had originally identified the _____ impurity in the May 7, 2002 Amendment to the NDA.

b(4)

It is the Sponsor's understanding as per the ICH Q3B(R2) Guidance, that "The level of any degradation product present in a new drug product that has been adequately tested in safety and/or clinical studies would be considered qualified." PENNSAID® has been investigated in eight Phase 3 clinical safety and/or efficacy trials since March 1994 and product stored for up to 24 months has been used in these trials (which represent a _____ PENNSAID® has been marketed in Canada (since May 2003), United Kingdom (since March 2001), Italy (since May 2003), Portugal (since 2004) and several Caribbean countries. PENNSAID® has been marketed with the same formulation, the same drug substance and excipients in quality and suppliers/manufacturers, and is prescribed with the same dosing regimen of 40 drops four times a day per knee as proposed in NDA 20-947. The Sponsor has also conducted the battery of three genotoxicity studies as per ICH [S2B (1997) Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals] with PENNSAID® that demonstrated the product is not genotoxic.

b(4)

Therefore, since the level of the _____ impurity present in PENNSAID® has been adequately tested in nonclinical safety and clinical studies, it would be considered qualified under ICH Q3B(R2).

b(4)

The identified impurity, _____

phenylacetic acid sodium salt), which has been demonstrated to be non-genotoxic. The Sponsor had a toxicology assessment prepared, which was not submitted to the NDA previously, since FDA had not identified this as a question until December 28, 2006. A copy of the report, "Assessment of Potential Risks Associated With Diclofenac and its _____ is provided as Appendix 9.3. The only difference between diclofenac and the impurity is the replacement of the _____ with _____ Chemically, this might be expected to _____ of the impurity as compared to diclofenac. A three dimensional structural comparison between

b(4)

b(4)

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

Dimethaid's Response:

Dimethaid acknowledges that the extractables from the HDPE bottle using the vehicle-control solution (72 mg) was above the USP <661> limit for _____ but below the limit for _____. Dimethaid is withdrawing the October 12, 2006 amendment providing for a _____ HDPE bottle, at this time, until further testing is completed.

b(4)

FDA's Response:

While the reason to revert back to _____ seems to be based on less amount of extractables from _____ compared to HDPE, this may not be an adequate justification for this change. Typically, _____ and results in more leachables such as ink, adhesives, environmental agents, etc. being migrated from outside of the containers compared to the HDPE containers. Also, even though the amount of extractables resulting from _____ was lower than that resulting from HDPE containers, the chemical nature of the extractables and their safety assessment should still be carried out in support of your proposal to continuing the use of _____. Although, in general, the degree of concern about the extractables and leachables associated with the topical route of administration is not very high, the fact that the formulation is a solution containing 45.5 % of a strongly extracting solvent, DMSO, coupled with the fact that it is a skin penetration enhancer that can potentially facilitate percutaneous absorption of otherwise non-absorbable chemicals exacerbates the safety concern with the use of this drug product. Therefore, identify the extractables and leachables from the drug product container closure system and provide a toxicological risk assessment for the potential exposures to these substances. This risk assessment should include characterization of the potential toxicity following exposure to any extracted compounds of the container closure system, including external ink and adhesives used for labeling. Data from published literature may be submitted in lieu of animal studies, if available.

b(4)

Discussion:

The Sponsor informed the Division that extractables and leachables will be identified from the _____ and the toxicity risk will be determined. Additionally, the Sponsor _____ and perform extractable and leachable tests and will provide 6 months of stability data at room temperature (25°C) in the resubmission. The Division advised the Sponsor that leachables would also have to be identified and quantified for the _____. Any stability updates would have to be submitted in a timely manner to conform to the GRMP framework.

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.

Dimethaid's Response & Question:

See response to No. 4 above—Dimethaid is withdrawing the October 12, 2006 amendment (to provide for a ——— HDPE bottle) and will launch and market the LDPE container-closure system, which meets the Agency guideline "Container Closure Systems for Packaging Human Drugs and Biologics, May 1999".

b(4)

Does the Agency agree with the Sponsor's plan?

FDA's Response:

See response to question 4.

Discussion

Questions 4 and 5 were discussed concurrently.

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.*

Dimethaid's Response & Question:

The requirement to characterize the dermal carcinogenic potential of PENNSAID® was not addressed in the August 7, 2002, non-approvable letter. In fact, carcinogenicity testing has never been requested by the FDA in our entire 12 years of communication with FDA regarding Pennsaid product development until the most recent communication with the Agency in the AE letter of December 28, 2006.

PENNSAID® NDA 020-947 is a 505(b)(2) application relying on published peer-reviewed literature references and the Agency's finding of safety for the previously approved reference listed drug product per 21 CFR 314.54 to support the nonclinical safety of the active ingredient, diclofenac sodium. As the Agency is aware, diclofenac has been fully evaluated for toxicity and carcinogenicity in oral and topical products approved by the Agency and currently marketed. The excipients, glycerin, propylene glycol and alcohol are used in approved products for chronic dermal administration (including transdermal), as per the FDA Inactive Ingredient Database for Approved Drug Products. Dimethyl sulfoxide (DMSO) also appears on the Inactive Ingredient Database for several non-topical products and is also the active ingredient in RIMSO-50® (NDA 017-788), which was approved in 1978 for treatment of interstitial cystitis.

The June 28, 2006 complete response amendment, as required under 21 CFR 314.50(d)(5)(vi)(b), was updated with all new nonclinical information, not previously known to the Sponsor at the time of the August 7, 2001 NDA, including three new nonclinical genotoxicity studies conducted with PENNSAID® and new peer-reviewed, published literature on DMSO

(including dermal carcinogenicity studies) and its metabolites DMSO2 and DMS. It is Dimethaid's position that there is an adequate scientific basis to conclude that dermal carcinogenicity animal testing is not necessary for the safe use of the product, and such information was provided in the June 28, 2006, complete response amendment.

This rationale has briefly been re-summarized here. An animal toxicity study (in Rhesus monkey) has been identified in which DMSO was the test chemical (Vogin et al., 1970). DMSO was used as a negative control in a two-year rat carcinogenicity study (Norpoth et al., 1986, 1988) and in a 3-month Tg.Ac transgenic mice study (Smith et al., 2003). In both studies, DMSO did not induce tumor formation. In a long-term (74–87 weeks) animal study (Rhesus monkeys), DMSO was administered orally or dermally at doses greater than 100 times the maximum clinical dose of Pennsaid®, and no evidence of tumors or preneoplastic changes were observed following histopathology of the surviving animals (Vogin et al., 1970). DMSO has been demonstrated to reduce tumors produced by known carcinogens or tumor promoters (Slaga and Fischer 1983; McCabe et al., 1986; O'Dwyer et al., 1988; Fletcher and Dennis, 1967; Iversen et al., 1981). DMSO was also tested using in vitro neoplastic transformation studies; at concentrations of 0.0625–2% in the culture medium, DMSO did not induce neoplastic transformation in Syrian hamster embryo (SHE) cells using a clonal assay (Heidelberger et al., 1983) and did not induce neoplastic transformation at doses up to 5000 µg/mL in either a 24-hour or 7-day exposure regimen (LeBoeuf et al., 1996). It can be concluded from all the in vivo animal studies that DMSO did not induce neoplastic lesions or tumors following topical, subcutaneous or oral administration.

The combined weight of the dermal and other animal studies, in conjunction with the reports of DMSO's lack of mutagenicity and the findings that it does not induce preneoplastic transformation in vitro, is sufficient to support the presumption that repeated DMSO administration would not be carcinogenic.

Study	Source	Dose	Route of Administration
2-Year Rat Oral Study Of Diclofenac	Voltaren NDA (RLD)	Up to 2 mg/kg/day	Oral
2 year Mouse Oral Study of Diclofenac	Voltaren NDA (RLD)	Up to 0.3 mg/kg/day (males; 1 mg/kg/day (females)	Oral
2-Year s.c. Rat Study (with DMSO)	Norpoth et. al., 1986, 1988	0.25 mL DMSO applied once/week	Subcutaneous
12 week Tg.AC Study of DMSO	Smith et. al., 2003	3 times a week	Topical
74 – 87 week Monkey (oral/topical) study with DMSO	Vogin et. al., 1970	90% DMSO: 1, 3 and 3 mL/kg b.w.	Oral and Topical

Three new PENNSAID® mutagenicity studies, conducted for the Sponsor and submitted in the

June 28, 2006 NDA resubmission, showed no indication of mutagenic properties of PENNSAID® (see Table 5 below).

Table 5: Mutagenicity Studies on Pennsaid®

Type of Study	Methods Used	Dose Range	Effect	Reference/ Date
In vitro non-mammalian cell system	Mutagenicity study of Pennsaid® in the Salmonella Typhimurium reverse mutation assay	100–5000 µg Pennsaid®/plate	No mutagenic effect was observed for Pennsaid® tested up to 5000 µg/plate in any of the 5 test strains in two independent experiments with or without metabolic activation	(Study No. 17623) 2004
In vitro mammalian cell system	Assessment of clastogenic activity of Pennsaid® in cultured human peripheral lymphocytes	Pennsaid® at concentrations 625–5000 µg/mL medium	Pennsaid® tested in the presence and absence of metabolic activation revealed no indications of mutagenic properties with respect to chromosomal or chromatid damage	(Study No. 17625) 2005
In vivo mammalian system	Micronucleus test of Pennsaid® in bone marrow cells of the NMRI mouse by oral administration	3, 6, 12 mL Pennsaid®/kg b.w.	Pennsaid® tested up to the maximum tolerated dose of 12 mL/kg b.w., p.o., showed no mutagenic properties at two tested sampling times of 24 and 48 hrs	(Study No. 17626) 2005

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Therefore, the Sponsor's view is that the Agency's proposed labeling, "Long-term studies in animals have not been performed to evaluate the carcinogenic potential of PENNSAID® or dermal administration of diclofenac" (December 20, 2006), is sufficient for approval.

Does the Agency agree with the Sponsor's response?

FDA' Response:

No. Dermal carcinogenicity studies with the drug product formulation should be completed since studies previously completed via the oral route of administration do not provide an adequate assessment of the potential dermal carcinogenicity. Given the use of DMSO, a novel excipient and penetration enhancer, these studies should be completed with the drug product formulation and include an arm containing DMSO alone at the highest concentration tested.

Prior to initiation of dermal carcinogenicity studies, you are encouraged to submit your study protocols to the Division and obtain concurrence from the Executive Carcinogenicity

Assessment Committee (eCAC). Please refer to the following guidance document: Carcinogenicity Study Protocol Submissions (May 2002), which is available on the CDER website at the following location: (<http://www.fda.gov/cder/guidance/4804fnl.pdf>).

The literature references cited either were not performed for an adequate duration or did not contain adequate information to support the long-term safety of your drug product. The study by Vogin et al., 1970 is a chronic toxicology study and while supportive of a lack of carcinogenic findings, it is much too short of a study and with too few animals to characterize DMSO's carcinogenic potential. The two studies by Norpoth et al. 1986 and 1988, used only one dose level of DMSO (as a control for the compound of interest) and did not characterize the types of lesions found. That data also indicates that there may be an increase in sarcomas (unidentified tissue type and location) with DMSO 0.25 mL sc injection in the neck once weekly for 2 years. The study by Smith et al. 2003 was also too short (12 weeks) to determine carcinogenicity potential.

These and other studies submitted in the resubmission were deficient with regards to one or more of the following aspects:

- **verification of the dose administered**
- **duration of the studies and number of animals studied**
- **toxicological and histopathological analysis**
- **statistical analysis of results**
- **toxicokinetic analysis**

Please refer to the following ICH Guidances for Industry:

- **S1A Testing for Carcinogenicity of Pharmaceuticals (June 1997)**
<http://www.fda.gov/cder/guidance/1854fnl.pdf>,
- **S1B Carcinogenicity Study Protocol Submissions (May 2002)**
<http://www.fda.gov/cder/guidance/4804fnl.pdf>, and
- **S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals (March 1995)**
<http://www.fda.gov/cder/guidance/ichs1c.pdf>.

Although we generally seek to identify all deficiencies during the initial review period, we sometimes become aware of deficiencies only during a subsequent review period. It would be inconsistent with section 505(d) of the FFDCA and FDA regulations to approve an application despite an applicant's failure to address deficiencies solely because those deficiencies were identified only after issuance of a complete response letter.

Discussion:

The Sponsor informed the Division that there is abundant and consistent information in the literature to support the non-carcinogenicity of PENNSAID's ingredients, including DMSO. The Sponsor also noted their intention to reference the dermal carcinogenicity information found in the approved drug product labeling for Solaraze®. The Division noted that the Sponsor may reference other data; however, they must provide information

to establish that the reliance on such data is scientifically appropriate. If such a pertinent relationship could not be established, then a dermal carcinogenicity study will need to be conducted. The Division advised the Sponsor to ensure that if they intend to rely on literature or other studies for which they do not have right of reference, they must provide adequate patent certification as indicated in 21 CFR 505(b)(2).

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.*

Dimethaid's Response & Question:

The original August 7, 2001 NDA (see Volume 3 of 130, Section 4.2.8.4, pages 143 – 171) contained the Photostability study report, conducted as per ICH Q1B Photostability Testing of New Drug Substances and Products (November 1996). During the review of the original August 7, 2001 NDA (as reflected in the NA letter) and the June 28, 2006 complete response amendment, no deficiency of conduct or conclusions of this report was communicated to the Sponsor. The report concluded that irradiation of PENNSAID® in its immediate packaging _____ and LDPE cap) showed that PENNSAID® was effectively protected from photodegradation. No change in color, UV absorbance (440 nm) or HPLC chromatograms was observed between the control and exposed samples.

b(4)

Furthermore, the August 7, 2001 NDA included two Phase 1 skin safety clinical trials: A Skin Photoirritation Study of Pennsaid, Study No. 103-93-2 (see Volume 12 of 130, page 214) and A Modified Draize Photosensitization Study of Pennsaid (see Volume 13 of 130, page 100). These studies demonstrated the skin photoirritation and photosensitization potentials of PENNSAID® to be negligible.

Thus, it is the Sponsor's understanding that the appropriate photostability studies have been performed and therefore no additional studies are needed. Does the Agency agree?

FDA's Response:

The Agency requires additional information in order to determine if the photostability studies and safety data provided to date are adequate. Provide data to demonstrate that the impurities detected in the photodegradation studies do not exceed the ICHQ3B thresholds for identification and safety qualification.

If any of the identified peaks contain structural alerts for mutagenicity, additional studies would be required to provide adequate safety qualification. Adequate safety qualification for any potential genotoxic impurities should include a minimal genetic toxicology screen (two in vitro genetic toxicology studies, point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay. Should this qualification produce positive or equivocal results, the impurity specification should be set at _____ or otherwise justified. Justification may require an assessment for

b(4)

carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

Discussion:

The Sponsor informed the Division that it found unidentified degradants only in exposed products and thought the previous studies indicating stability in the closed container were sufficient. The Division acknowledged that those studies were acceptable as evidence of stability of the drug product in the container, but since this product is applied to the skin and left uncovered, it is important to know from a toxicological perspective what degradants would be present on the skin if PENNSAID is exposed to the sun. The Division asked the Sponsor to provide identification and quantification of the already known degradant peaks from the stability studies as the first step. This would be followed by genotoxic and acute toxicity studies, conducted by the Sponsor or obtained from the scientific literature if available. The Sponsor suggested that the area exposed to PENNSAID could be covered and that would be included in the labeling as per ICH Q1B. The Sponsor asked if the same degradants were shown to be found in the approved topical diclofenac product (Solaraze) in the same range or higher levels, could the Sponsor conduct an appropriate biobridge study to rely on the Agency's finding of safety for these degradants also present in Solaraze. The Division indicated that it would consider such an argument, should the data be provided; however, final determination of the adequacy of the data could only be provided upon review of the data.

ACTION ITEMS

- 1. The Sponsor is to provide protocol design to substantiate that after 20 minutes of applying PENNSAID the permeability of the skin is no longer altered and that subsequent exposure to environmental toxins is no longer enhanced.**
- 2. Sponsor agreed to conduct the genotoxicity studies of the degradant.**
- 3. The Sponsor is to provide identification and quantification of the already known degradant peaks from the stability studies.**

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

/s/

Paul Balcer
3/1/2007 06:56:19 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-947

DISCIPLINE REVIEW LETTER

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) submitted 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 also refer to your submissions dated August 17, and October 25, 2006.

The Division of Medication Errors and Technical Support (DMETS) has reviewed your submission and has the following comments on the graphic design:

Remove the graphic design of a teardrop from the container and carton labels. The teardrop looks like an eye drop rather than a topical product. We are concerned that having this teardrop on the labels and labeling might encourage users to think that it may be used via the ophthalmic route.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

**If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager,
at 301-796-1173.**

Sincerely,

{See appended electronic signature page}

**Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
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/

Parinda Jani
12/14/2006 08:30:11 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **20-947** Supplement # Efficacy Supplement Type **SE-**

Proprietary Name: **PENNSAID® Topical Solution (1.5% w/w diclofenac sodium)**
Established Name: **diclofenac sodium USP**
Strengths: **1.5% w/w diclofenac sodium solution**

Applicant: **Dimethaid International, Inc.**
Agent for Applicant (if applicable): **Frederick N. Ballantyne (U.S. Agent)**
2220 Chalkwell Dr.
Midlothian, VA 23113-3884

Mimi Brennan, Director Clinical Research and Regulatory Affairs (Representative for Dimethaid International, Inc.)
Nuvo Research, Inc.
7560 Airport Rd., Unit 10
Mississauga, Ontario, L4T 4H4, Canada

Date of Application: **June 28, 2006, August 7, 2001, December 15, 1997**
Date of Receipt: **June 28, 2006, August 8, 2001, January 8, 1998**
Date clock started after UN:
Date of Filing Meeting:
Filing Date: **N/A**
Action Goal Date (optional): User Fee Goal Date: **December 28, 2006**

Indication(s) requested: **Topical treatment for relief of the signs and symptoms of osteoarthritis of the knee(s)**

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:
(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) **3S**
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health) small business

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the*

User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? Not Years
YES, specified NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **IND 42,773**
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) June 5, 2000 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: **In the February 13, 2006 correspondence to the Sponsor, the Division agreed for Sponsor to provide the draft labeling in PDF format at the time of NDA resubmission, with the final agreed upon labeling submitted in SPL format.**

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no; did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 28, 2006

NDA #: 20-947

DRUG NAMES: PENNSAID® Topical Solution (1.5% w/w diclofenac sodium)

APPLICANT: Dimethaid International, Inc.

BACKGROUND: This is a complete response to the August 7, 2002 Non approval letter.
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Jeff Siegel, M.D., Larrisa Lapteva, M.D., Dan Mellon, Ph.D., Asoke Mukherjee, Ph.D., Dionne Price, Ph.D., Thomas Permutt, Ph.D., Suresh Doddapaneni, Ph.D., David Lee, Ph.D. and Paul Z. Balcer

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
OPS:
Regulatory Project Management:

Reviewer

Larrisa Lapteva, M.D.
Jeff Siegel, M.D. (Team Lader)
Thomas Permutt, Ph.D.
Asoke Mukherjee, Ph.D.

Sue Ching Lin

David Lee, Ph.D.

Carolanne Carrier

Paul Z. Balcer

Other Consults:

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO
If no, explain:

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

• GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

• Establishment(s) ready for inspection? YES NO

• Sterile product? YES NO

If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments: Missing SPL.

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Paul Z. Balcer
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): 19-201 Voltaren®

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b) and (c).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. **NO.**

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **This application provides for a change in dosage form, from delayed-release tablets to topical solution.**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
 - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
- NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
 - Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
 - 21 CFR 314.50(i)(1)(ii): No relevant patents.
 - 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

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/s/

Paul Balcer
12/4/2006 01:02:15 PM
CSO

From: Balcer, Paul
Sent: Friday, October 06, 2006 3:32 PM
To: 'Mimi Brennan'
Cc: Stradley, Sara
Subject: NDA 20-947 PENNSAID - Clinical Information Request.

Follow Up Flag: Reply
Due By: Sunday, October 15, 2006 12:00 AM
Flag Status: Flagged

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following clinical information request:

- 1) Determine proportions of patients with changes from normal to three levels of abnormal (ULN-<1.5 ULN, ≥ 1.5 ULN - <3 ULN, and ≥ 3 ULN) for AST, ALT, GGT, total Bilirubin, and creatinine in **each of the combined arms from seven controlled trials** (similar to the newly submitted Table 3.2 in the most recent submission-response to our IR).
- 2) For study PEN 112E (12 months trial) calculate proportion of patients with a) 5 mm increase in mean blood pressure (as was done in study PEN-112) and b) calculate the proportion of patients with hypertension as defined by either a 20% increase in diastolic BP from baseline (at any time during the study) or an increase in blood pressure to >150/100 at any time during the study.
- 3) For study PEN-03-112, perform sensitivity analysis for the 3 endpoints that reflect dimensions on the WOMAC scale (pain, physical function, and stiffness) while excluding patients who failed to score more than a minimal amount of items (as per Guide). For this analysis, include only patients who completed all items on WOMAC scale and those who completed minimal required amount of items (at least 4 for pain, 14 for physical function and 1 for stiffness).

Please provide us with the above information no later than **October 15, 2006**.

Best regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.

Bldg. 22 Rm. 3145
Silver Spring, MD 20993-0002
Tel.: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer

12/4/2006 09:11:42 AM

CSO

C:\Documents and Settings\balcerp\Desktop\NDA 20-947\NDA20947\Biostatistics\IR092206.txt
BlankFrom: Balcer, Paul
Sent: Friday, September 22, 2006 9:57 AM
To: 'Mimi Brennan'
Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) -
Biostatistics Information Request.

Importance: High

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing the Module 5 (Clinical) section of the application and are requesting the following clarification:

Approximately 40 patients were excluded from the original "intent-to-treat" analysis of study 109US because of "invalid" final assessments. For each patient explain how the assessment was invalid. Also explain how such patients have been incorporated into the new analysis. That is, were the "invalid" data used, or have other values been imputed?

We ask for a prompt response to our inquiries so that we may continue our review. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
12/4/2006 08:57:55 AM
CSO

From: Balcer, Paul
Sent: Wednesday, November 08, 2006 11:48 AM
To: 'mbrennan@nuvoresearch.com'
Subject: NDA 20-947 PENNSAID - Clinical Information Request - Request for gender identification for a death narrative in study 10293-1, Section 12.3.2 (p.154)

Importance: High

Follow Up Flag: Reply
Due By: Thursday, November 09, 2006 5:00 PM
Flag Status: Flagged

Dear Ms. Brennan:

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

We are seeking a gender identification in a death narrative for patient #206 in the study 10293-1, under Item 8, section 12.3.2 on page 154.

We ask that you provide us with the above information no later than **Thursday, November 9, 2006**. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 22 Rm. 3145
Silver Spring, MD 20993-0002
Tel.: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
12/1/2006 03:44:33 PM
CSO

From: Balcer, Paul
Sent: Monday, November 06, 2006 2:56 PM
To: 'mbrennan@nuvoresearch.com'
Subject: NDA 20-947 PENNSAID - Clinical Information Request - Cases of retinal or post vitreous detachments.

Importance: High

Follow Up Flag: Reply
Due By: Monday, November 13, 2006 3:00 PM
Flag Status: Flagged
Expires: Thursday, December 28, 2006 5:00 PM

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following clinical information request. Please provide the following:

1. Narrative of the post-vitreous detachment case in pt # 69016 from study PEN-03-112, including her previous eye and other past medical history.
2. Narrative of retinal detachment case in pt # 25231, including that patient's previous history (if the company has more information other than what it reported on p 117 in ISS).
3. Formal response from Dimethaid specifically about **any other cases of retinal or post vitreous detachment** either during their development program (especially cases that were coded as "retinal disorder" in COSTART) or from post-marketing experience from UK, Canada, and other countries where the drug was approved. If there were any such cases in addition to the two mentioned above, we ask them to provide narratives of those cases.

We ask that the responses to the above inquiries be submitted to us no later than **November 13, 2006**. If you have any questions, please contact me.

Regards,,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bld. 22 Rm. 3145
Silver Spring, MD 20993-0002
tel. (301) 796 1173

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paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
12/1/2006 03:22:56 PM
CSO

From: Balcer, Paul
Sent: Thursday, November 02, 2006 8:01 AM
To: 'mbrennan@nuvoresearch.com'
Subject: FW: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - CMC Information Request and labeling comments.

Importance: High

Follow Up Flag: Reply
Due By: Tuesday, November 07, 2006 12:00 AM
Flag Status: Flagged

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

Additionally, please refer to the October 25, 2006 submission, Appendix 2.

We are reviewing your application and have the following CMC information requests:

1. The dosing directions require that the dose be measured by drops. Provide the volume and the amount of the active ingredient contained in each application of 40 drops. Provide data showing that a consistent volume is applied to the knee.
2. Please provide carton and container labeling in color versions.

Please provide above information no later than **Tuesday, November 7, 2006**. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 22 Rm. 3145
Silver Spring, MD 20993-0002
Tel.: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer

12/1/2006 03:27:38 PM

CSO

From: Balcer, Paul
Sent: Wednesday, November 15, 2006 10:36 AM
To: 'mbrennan@nuvoresearch.com'
Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - CMC Information Request in regards to the October 27, 2006 response from Diemthaid.

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following CMC comments and information request:

In addition to the test on "removable torque," which was included in the drug product specification in response to the FDA comments, the revised regulatory specification that was submitted on pages 15-16 of the 10/27/06 amendment appears to be different from the drug product specification submitted in the May 7, 2002 amendment:

1. The 5/7/02 amendment includes an identification test by UV diode array spectral profile, in addition to the HPLC retention time.
2. The analytical method used for dimethyl sulfoxide assay was a GC method instead of HPLC.

Please revise the drug product specification including the UV identification and the correct method for dimethyl sulfoxide assay.

The revised drug product specification may be submitted in the same amendment with the requested results for USP <671> and USP <661> water permeation study, if the results have not been submitted yet.

Please provide above information no later than **Friday, November 17, 2006**. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 22 Rm. 3145
Silver Spring, MD 20993-0002
Tel.: (301) 796 1173
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E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
11/15/2006 10:56:46 AM
CSO

Sent: Friday, October 20, 2006 2:28 PM
To: 'Mimi Brennan'
Subject: NDA 20-947 PENNSAID - Clinical Information Request - Post Marketing Adverse Event Reports and labeling from the United Kingdom and Canada

Importance: High

Follow Up Flag: Reply
Due By: Wednesday, October 25, 2006 5:30 PM
Flag Status: Flagged

Attachments: Summ_prod_characteristics.pdf; Canada_product_mongraph.pdf

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following clinical information request:

1. Please direct us to the adverse events in the June 28, 2006 submission that occurred since marketing of the product in the United Kingdom and Canada.
2. Please verify that the two attached files are package inserts for the Canadian and UK labels for PENNSAID and if not, provide us with the most recent labeling.

We ask that you provide us with the above information no later than Wednesday, October 25, 2006. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 22 Rm. 3145
Silver Spring, MD 20993-0002
Tel.: (301) 796 1173
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E-mail: paul.balcer@fda.hhs.gov



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/s/

Paul Balcer
10/20/2006 02:54:17 PM
CSO

Sent: Friday, October 20, 2006 1:02 PM
To: 'Mimi Brennan'
Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - CMC Information Request and labeling comments.

Importance: High

Follow Up Flag: Reply
Due By: Wednesday, October 25, 2006 5:30 PM
Flag Status: Flagged

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following CMC comments and information request:

1. USP <671> testing was requested because it could be used to demonstrate that the proposed container closure system is sufficiently tight to deter solvent loss. Although it is typically applied to the testing of containers for capsules and tablets, the principles are relevant to the assessment of permeation of liquids from the containers. Therefore, provide a summary data on container closure permeation based on the principles of USP <671>. Refer to Section III.F.2 and Table 6 (under protection) of "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics" for liquid-based topical products.
2. The results of USP <661> testing, as submitted in the 10/12/06 amendment, did not include information on water permeation. Since this test is for the determination of container permeation, provide the test results for water permeation.
3. Drug product stability data contained in the 8/17/06 amendment did not include information on the deliverable volume for all stability batches. Since this is a stability-indicating attribute and a surrogate for solvent losses due to permeation and since it is listed in the stability protocols, provide testing results for all stability batches at release and at expiry.
4. Provide tabulated stability data for all the batches of the drug product that were used in support of the proposed expiration dating period of 36 months.
5. Inconsistencies were noted in reporting the test results of "removable torque" in the batch analysis and stability reports. Provide the results of

"removable torque" testing on all batches of the drug product listed in the NDA and revise the specifications (section D6) accordingly. Also, provide a justification of the acceptance criteria for this test based on the requested results of USP <671> or equivalent testing (see comment 1).

6. The following comments pertain to the labeling of the drug product:

(a) Title and Description sections of the package insert:

(1) The proprietary name and established name should be displayed as follows:

**Pennsaid® Topical Solution
(diclofenac sodium topical solution) 1.5% w/w**

Or

Pennsaid® (diclofenac sodium) Topical Solution 1.5% w/w

Increase the prominence of the established name to at least half that of the proprietary name. Please note that prominence includes a combination of font shape, size, font color, and overall visual appeal.

(2) Provide pharmacological/ therapeutic class in the "description" section as required in 21CFR 201.57(a)(v).

(b) Container and carton labels:

(1) The proprietary name and established name should be presented as stated in (a)(1) above.

(2) Use of color contrasts in the proprietary name to highlight "NSAID" portion of the proprietary name is not acceptable. Use only one color for the proprietary name. The color for the established name appears to be too light. As specified in 21 CFR 201.10(g)(2), the established name shall have a prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See comment above.

(3) Include a bar code on the container and carton labels as required in 21 CFR 201.25 and FDA "Guidance for Industry, Bar Code Label Requirements -- Questions and Answers."

(4) Increase the prominence of the wording _____

b(4)

(5) The side panels appear very cluttered and hard to read whereas the main display panel contains large unused area that contains a drawing of a big droplet. Bring down the clutter on the side panels by moving some information on the main display panel.

Please provide above information no later than **Wednesday, October 25, 2006**.
If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 22 Rm. 3145
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/s/

Paul Balcer
10/20/2006 01:31:09 PM
CSO

Sent: Monday, September 25, 2006 4:33 PM
To: 'Mimi Brennan'
Subject: NDA 20-947 PENNSAID - Response to proposed changes to the container.

Importance: High
Sensitivity: Confidential

Dear Ms. Brennan,

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

Please also refer to our telephone conversation of September 12, 2006 in which you inquired about the changes to the bottle and a proposed switch from the _____ to the HDPE plastic. The ONDQA has reviewed your proposal and requests that you provide the following information:

b(4)

1. Justification of the proposed changes.
2. Description of the proposed container closure systems (e.g., materials of construction, manufacturer, product code, physical description etc.)
3. Assurance of safety of all proposed packaging components by reference to appropriate 21CFR food additive regulations.
4. USP <661> testing results for the proposed packaging components, using the drug product vehicle as the extraction medium.
5. USP <671> testing results
6. At least three months of stability data should be provided for the drug product packaged in the proposed container closure systems (all packaging sizes) and stored under long-term and accelerated conditions. The stability studies should be performed with the drug product stored in inverted and upright orientations.

You may choose to submit the proposed changes to the NDA only if the requested information is available at this time.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration

10903 New Hampshire Ave.
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/s/

Paul Balcer
10/4/2006 03:15:05 PM
CSO

From: Balcer, Paul

Sent: Thursday, August 24, 2006 4:13 PM

To: 'mbrennan@nuvoresearch.com'

Cc: Davies, Kathleen; Stradley, Sara

Subject: NDA 20-947 PENNSAID (1.5% w/w diclofenac sodium) - CLINICAL Information Request (#3).

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing the Module 5 (Clinical) section of the application and are requesting phone and fax numbers for the following sites:

Site # (Name and Address)	Protocol #	Number of subjects	Indication
Site #32 PI: Dr. James Lai Study coordinator: _____ 620-943 West Broadway Vancouver, BC, Canada, V5Z1K3	PEN-03-112	19	Relief of signs and symptoms of osteoarthritis of the knee
Site #44 PI: Dr. Stewart Silagy Study coordinators: _____ _____ Hill Top Research Inc. A-236 Osborne Street, Winnipeg, MB, Canada, R3L2W2	PEN-03-112	50	Relief of signs and symptoms of osteoarthritis of the knee
Site #71 PI: Dr. Sam Miller Study coordinators: _____ Sam Clinical Research Center 300-7711 Louis Pasteur Drive	PEN-03-112	39	Relief of signs and symptoms of osteoarthritis of the knee

b(4)

b(4)

b(4)

San Antonio, TX, USA, 78229			
Site #66, Warwick, RI PI: Dr. David L. Fried Study coordinator: <hr/> Omega Medical Research 400 Bald Hill Road Warwick, RI, USA, 02886	PEN-03-112	64	Relief of signs and symptoms of osteoarthritis of the knee

b(4)

We ask for a prompt response to our inquiries, no later than August 29, 2006, so that we may continue our review. If you have any questions, please contact me, or Kathleen Davies, M.S. (after August 25, 2006).

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
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/s/

Paul Balcer

8/24/2006 04:36:12 PM

CSO

From: Balcer, Paul
Sent: Wednesday, August 23, 2006 9:16 AM
To: 'mbrennan@nuvoresearch.com'
Cc: Daviès, Kathleen

Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - CLINICAL Information Request.

Importance: High

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing the Module 5 (Clinical) section of the application and are requesting the following additional information for study PEN-03-112:

1. Patient Disease characteristics

- 1.1 Please provide a table listing the following baseline characteristics, by study arm:
- i. mean disease duration
 - ii. average age at disease onset
 - iii. prior and at baseline NSAID use
 - iv. prior and at baseline use of analgesics (including opioid analgesics) and other anti-rheumatic drugs
 - v. proportion of patients in each group with morning stiffness
 - vi. proportion of patients in each group with starting stiffness
 - vii. average frequency of Tylenol use prior to the study enrollment and at baseline
 - viii. prior use of topical knee treatments
 - ix. proportion of patients with diabetes,
 - x. proportion of patients with depression
 - xi. proportion of patients applying for disability
 - xii. proportion of patients from different geographic regions in each arm (US and Canada)
 - xiii. identify which study centers are tertiary care centers vs. less-than-tertiary centers and show the proportion of patients from both types of centers in each study arm
- 1.2 Clarify if Table 14.1. 11 refers to "during the study" or "prior to the study" medication use

- 1.3 Provide a listing of all the drugs unified in the “anti-inflammatory and anti-rheumatic drugs” category for each study arm
- 1.4 Provide a listing of all the drugs unified in the “analgesics” category for each study arm
- 1.5 Provide a listing of ophthalmologic diseases (specify which) in each study arm. Along with it provide a listing of all the ophthalmologic products and indications for concomitant use of ophthalmologic products patient by patient, for each study arm
- 1.6 Provide a listing of all the antibacterial products as concomitant medications and their indications for use for each study arm

2. Efficacy analysis:

To aid in the interpretation of your data conduct and submit the following sensitivity analyses:

- 2.1 Conduct an analysis similar to the primary analysis but that includes only study completers in all five study arms (for both primary and secondary endpoints).
- 2.2 Indicate the proportion of patients who failed to score more than a minimal amount of question(s)/item(s) in each of the dimensions of the WOMAC scale (indicated in *The WOMAC Osteoarthritis Index-User's Guide III*) and whose scores had to be imputed by your modified approach per each study arm. Provide a spreadsheet enabling the conduct of an appropriate sensitivity analysis.
- 2.3 Characterize drop outs (demographics at baseline, mean scores on primary endpoints and secondary endpoints at baseline and at final visits, use of concomitant rescue medications and prohibited medications [acetaminophen, and analgesics, and anti-inflammatory and anti-rheumatic drugs]) for each study arm and total.
- 2.4 Conduct an ITT analysis of the proportion of responders (patients who achieved your pre-specified clinically meaningful difference) in each of the primary and secondary endpoints.
- 2.5 Perform an ITT analysis of the proportion of responders by study arm using the OMERACT-OARSI revised responder criteria (Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis and Cartilage*, 2004 (12) pp 389-399). For responders specify the proportion who meet criteria for: 1) high improvement in pain or physical function $\geq 50\%$ and absolute change more $\geq 20\%$ and 2) those meeting criteria for response based on 2 out of 3 indicated criteria.
- 2.6 Provide subset analyses for the mean values (your original ITT population) and proportion of OMERACT-OARSI (see 2.5 above) responders for the following variables:
 - i. Gender (F / M)
 - ii. Age (35-55, 56-75, 76 and older)
 - iii. Race (white and other)
 - iv. Weight, kg (≤ 80 , 81-90, ≥ 90)

- v. Prior NSAIDs use (yes, no)
- vi. Concurrent NSAIDs use (yes, no- for those who used prohibited medications)
- vii. Concurrent use of psycholeptics, psychoanaleptics (yes, no)
- viii. Concurrent use anti-rheumatic/anti-inflammatory drugs (yes, no)
- ix. Concurrent use of analgesics (yes, no)
- x. Geographic region (US, Canada)
- xi. Tertiary vs less than tertiary
- xii. Patients applying for disability (yes, no).

3. Safety analysis

In certain instances your definition of CSA exceeds level that may nonetheless be of clinical concern. For example, your definition of clinically significant abnormality (CSA) in Table 38 (page 108) of the study indicates that liver enzymes are considered CSA only if the value exceeds 3 UNL. Such values are substantially out of range with what would be considered clinically abnormal in clinical practice. Further, values for CSA in platelet counts, hemoglobin, white blood cell counts and other parameters are also out of range with what would typically be considered worrisome in medical practice. To assist in our assessing the safety of your product:

- 3.1 Provide analyzable spreadsheets for **all safety assessments** (including lab values, occurrence of adverse events, and changes in vital signs) at the baseline, 4 weeks, 8 weeks and final study visits for **each study arm**. Provide analyzable spreadsheet/dataset with ocular assessments.
- 3.2 Re-categorize the clinically significantly abnormal (CSA) shifts for each of the liver enzymes, creatinine and bilirubin to the following: 1) ULN-<1.5 ULN; 2) ≥ 1.5 -<3ULN, 3) ≥ 3 ULN. Compute the proportion of patients with these changes in each of the study arms and present in a table.
- 3.3 re-categorize the clinically significantly abnormal (CSA) shifts for other parameters to the following CTC-derived CSA values:
 - hemoglobin- ≤ 100 g/L for females and ≤ 115 g/L for males,
 - platelet count- ≤ 100 or $\geq 500 \times 10^9/L$,
 - WBC - ≤ 3.5 or $\geq 13.0 \times 10^9/L$,
 - 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

For each study arm, compute proportion of patients showing change: 1) from normal-to-abnormal, 2) from normal-to-newly defined CSA, and 3) from normal-to-previously defined CSA for **each of the study arms** and present in a table with the following format:

Baseline value	Changes to		
	Abnormal	Newly Defined CSA	Previously Defined CSA
Normal			
Abnormal			

- 3.4 For each study arm, provide the number of patients with hypertension as defined by either a 20% increase in diastolic blood pressure from baseline or an increase in blood pressure to > 150/ 100 at final study visit.
- 3.5 The list of protocol violations (Table 10, pp 53-54, Study #PEN-03-112) indicates that 89 patients did not complete the final ophthalmologic exam. Provide the proportion of non-completers per each arm. Table 37 on page 107 of the study report depicts the numbers relative to all patients in the group. Conduct additional analyses restricted to those patients who completed the final ocular exam reporting the rate of ophthalmologic AEs
- 3.6 Table 33 on page 94 of the study report indicates that there were 5 rectal hemorrhages in the PENNSAID+oral Diclofenac group and 1 rectal hemorrhage in the PENNSAID+oral placebo group as opposed to no rectal hemorrhages occurring in other treatment groups. None of these cases were included in the listings of serious adverse events. Please provide a narrative description for each of the 6 cases.

INTEGRATED ANALYSIS OF SAFETY

1. There is a discrepancy in your calling your product "lotion" in some studies (100-89, 101-89-2, 103-93-2, 104-93-3, 107-96, and RA-CP-109US) and "solution" in other studies (RA-CP-109US, PEN-03-112, PEN-03-112E). It is unclear whether they represent the same product. Provide clarification on the composition and solubility of your product in the forms it was used in different studies as well as explanation of the two terms (lotion vs solution) used in the description of your trials.
2. **Exposure.** The following information is required to evaluate the exposure to product components:
 - 2.1 provide mean (SD), median, and range of duration of exposure in days for vehicle control (DMSO 45.5%), placebo control (2.3% or 4.5%DMSO), and topical diclofenac arms for all of the 7 controlled studies
 - 2.2 provide the numbers of patients by intervals of exposure for vehicle control (DMSO 45.5%), placebo control (2.3% or 4.5%DMSO), and topical diclofenac arms for all the 7 controlled studies (by analogy with Table 7 on page 20 in your Integrated Summary of Safety)
 - 2.3 Table 7 on page 20 of your ISS indicates that 14 out of 911 patients from the combined arm of all patients exposed to PENNSAID had no available data to assess their duration of exposure. Provide the number of patients with unavailable data for all other combined arms.

3. **Laboratory tests.** List all laboratory tests and safety assessments (ocular etc) that were obtained in the 7 controlled studies with separate lists for each trial. If no laboratory studies or other safety assessments were obtained in certain trials- that should be stated explicitly. Provide the spreadsheets with laboratory values and vital signs at baseline, 4 week (where appropriate), and 12 week final visits for the 6 combined arms in all 7 studies, from which mean and median changes in values can be calculated.
 - 3.1 For each of the laboratory parameters and vital signs, compute the mean change from baseline to 4 weeks, or 12 weeks assessments.
 - 3.2 Re-categorize the CSA lab values as above (Safety section 3.3 for study PEN-03-112 above) and compute proportion of patients with newly defined CSA values and your previously defined CSA, for each lab test showing proportion of patients changing: 1) from normal-to-abnormal, 2) from normal-to-newly defined CSA, and 3) from normal-to-previously defined CSA for each of the combined arms in the format of the table shown below.

Baseline value	Changes to		
	Abnormal	Newly Defined CSA	Previously Defined CSA
Normal			
Abnormal			

- 3.3 Submit a revised version of Table 45, p.65 in your ISS that captures **all the laboratory tests** that were measured in the controlled studies. Include in the analysis of laboratory parameters only patients in whom those laboratory tests were measured.
 - 3.4 Submit a revised version of Tables 47, 48, pp 68-69 in you ISS that includes the Vehicle control arm (45.5% DMSO).
4. **Adverse events.** For combined data from all seven controlled trials in the 6 combined arms provide analyzable spreadsheets from which the incidence of all the AE (including deaths and serious and severe AE) could be calculated as well as the following:
 - 4.1 Number of **severe adverse events** (and narratives) per each of the combined arms, please comment in the narratives whether the patients were continued in the study or withdrawn from the study after the AE occurrence.
 - 4.2 Provide a table with proportion of patients who dropped out of the studies due to severe adverse events (in the format similar to Table 42 p 63 from your ISS).
 - 4.3 In Table 42, p 63 from your ISS, you showed that there were no drop outs due to cardiovascular adverse events in the study 108-97. However, your narrative on page 93 indicates that patient # 06-018 developed a serious adverse event (acute myocardial infarction) during the treatment with PENNSAID. Clarify whether that patient was discontinued from the study.
 - 4.4 Provide narratives of the serious adverse events occurring due to treatment with vehicle control (45.5% DMSO)
 - 4.5 For each combined arm, provide the number of patients with hypertension as defined by either a 20% increase in diastolic blood pressure from baseline or an increase in blood pressure to > 150/ 100 at final study visit.

5. For study PEN-03-112E provide analyzable datasets for all the safety assessments (lab tests, AEs, skin and ophthalmologic assessments).

The above information request is to be discussed at the upcoming August 31, 2006 teleconference. If you have any questions, please contact me, or Kathleen Davies, M.S. (after August 25, 2006).

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
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/s/

Paul Balcer

8/23/2006 11:54:30 AM

CSO

From: Balcer, Paul
Sent: Thursday, August 10, 2006 11:25 AM
To: 'Mimi Brennan'
Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - CMC Information Request.

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following CMC information request:

1. Provide mock-up container and carton labels. These labels should be presented in the sizes and colors proposed for marketing. (The 6/28/06 resubmission only provided labeling text.)
2. Provide drug product samples packaged in the proposed container closure systems (one bottle for each packaging size). These samples are for the reviewers to examine the products only, not for method validation purpose.

We ask for a prompt response to our inquiries so that we may continue our review. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
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/s/

Paul Balcer

8/10/2006 11:39:48 AM

CSO

From: Balcer, Paul

Sent: Monday, August 07, 2006 4:25 PM

To: 'Mimi Brennan'

Subject: RE: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - Biostatistics Information Request Clarifications.

Sensitivity: Confidential

Dear Ms. Brennan,

Thank you for sending us the questions from your biostatistician. The following answers were provided by our biostats. review team:

Q.1 Answer. We have no preference, either is acceptable.

Q.2 Answer. We mainly need the sums at endpoint, which are the primary variables. As we noted, however, these should include imputations where needed as well as an indication that the values were imputed.

Q.3. Answer. Please submit separate files for each study.

Q.4 Answer. Please send SAS "version 5 transport," such as would be written by LIBNAME SASV5XPT...; PROC COPY ...

Q.5 Answer. The same KEYVAR as in the already submitted "CRT" folder.

In regards to the MS Excel sheet for the 112 test data, it looks right, but it is hard to be sure as there appear to be no cases where imputation is needed among the test data. Please add variables PCHANGE1, etc., defined analogously to PAIN_F1; i.e., the change from baseline with imputation as needed.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
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Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

From: Mimi Brennan [mailto:mbrennan@nuvoresearch.com]
Sent: Thursday, August 03, 2006 4:45 PM
To: Balcer, Paul

Subject: RE: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium)
- Biostatistics Information Request
Importance: High
Sensitivity: Confidential

Dear Paul,

As we discussed this afternoon, here are the questions from our biostatistician:

1. Should we send the data in SAS 6.12 or SAS 8.2?
2. Do you require the total and change score of the primary efficacy variables across different visits as well as the individual item score?
3. Should we send one file containing both 112 and 109-US or separate files for each study?
4. Which type of data transfer is preferred: Zip password protected or SAS export?
5. What key variable should be included in the data set?

Please find attached an Excel sheet for the 112 test data. First worksheet contains the description of the variables and the second contains the test data. Please confirm if this is acceptable.

Thanks,

Mimi

-----Original Message-----

From: Balcer, Paul [mailto:paul.balcer@fda.hhs.gov]
Sent: Tuesday, August 01, 2006 12:38 PM
To: Mimi Brennan
Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - Biostatistics Information Request
Importance: High
Sensitivity: Confidential

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following biostatistical information request:

For studies 112 and 109-US provide an analytical data set on which key efficacy computations can be efficiently performed. All randomized patients should be represented. For all primary efficacy variables include

1. The value at the end of the study
2. The baseline value
3. The calculated change from baseline
4. The 4- and 8-week values
5. The imputed value for cases where the end-of-study value is missing, both by LOCF and BOCF

6. An indicator of whether the patient is included in the "ITT" and "per protocol" analyses presented in the NDA.

We ask for a prompt response to our inquiries so that we may continue our review. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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this page is the manifestation of the electronic signature.**

/s/

Paul Balcer
8/10/2006 11:24:46 AM
CSO

From: Balcer, Paul

Sent: Thursday, August 03, 2006 2:32 PM

To: 'Mimi Brennan'

Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) - CMC Information Request.

Importance: High

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following CMC information request:

(1) _____ is listed in the 6/28/06 resubmission with the following address:

However, the following address was provided in the 8/7/01 submission:

b(4)

Please provide information as to whether the same facility has been moved, or it is a new facility.

(2) Provide updated stability data on the drug product.

We ask for a prompt response to our inquiries so that we may continue our review. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
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Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer

8/10/2006 11:26:08 AM

CSO

From: Balcer, Paul

Sent: Tuesday, August 01, 2006 12:38 PM

To: 'Mimi Brennan'

Subject: NDA 20-947 PENNSAID Topical Solution (1.5% w/w diclofenac sodium) -
Biostatistics Information Request

Importance: High
Sensitivity: Confidential

Follow Up Flag: Reply
Flag Status: Flagged
Expires: Friday, December 29, 2006 12:00 AM

Dear Ms. Brennan:

Please refer to your June 28, 2006 amendment to the new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PENNSAID Topical Solution (1.5% w/w diclofenac sodium).

We are reviewing your application and have the following biostatistical information request:

For studies 112 and 109-US provide an analytical data set on which key efficacy computations can be efficiently performed. All randomized patients should be represented. For all primary efficacy variables include:

1. The value at the end of the study
2. The baseline value
3. The calculated change from baseline
4. The 4- and 8-week values
5. The imputed value for cases where the end-of-study value is missing, both by LOCF and BOCF
6. An indicator of whether the patient is included in the "ITT" and "per protocol" analyses presented in the NDA.

We ask for a prompt response to our inquiries so that we may continue our review. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
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Phone: (301) 796 1173
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E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer

8/1/2006 12:47:52 PM

CSO



NDA 20-947

Nuvo Research, Inc.
c/o Dimethaid International, Inc.
7560 Airport Rd.
Unit 10
Mississauga, Ontario
Canada, L4T 4H4

Attention: Mimi Brennan
Director, Clinical Research and Regulatory Affairs

Dear Ms. Brennan:

We acknowledge receipt on June 28, 2006 of your June 28, 2006 resubmission to your new drug application for PENNSAID® Topical Solution (1.5% w/w diclofenac sodium).

We consider this a complete, class 2 response to our August 7, 2002 action letter. Therefore, the user fee goal date is December 28, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

If you have any question, call me, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
Regulatory Healthcare Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Paul Balcer

7/12/2006 03:19:33 PM

ACTION PACKAGE CHECKLIST

BLA # NDA # 20-947	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: PENNSAID Established Name: diclofenac sodium USP Dosage Form: 1.5% w/w diclofenac sodium solution		Applicant: Dimethaid International, Inc. Frederick N. Ballantyne, U.S. Agent Mimi Brennan, Director Clinical Research and R.A, Nuvo Research, Inc.
RPM: Paul Z. balcer		Division: Anesthesia, Analgesia and Rheumatology Products
Phone # (301) 796 1173		
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): NDA 19-201
(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		Provide a brief explanation of how this product is different from the listed drug. This application provides for a change in dosage form, from delayed-release tablet to solution.
		<input type="checkbox"/> If no listed drug, check here and explain:
		Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.
		<input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: December 4, 2006
❖ User Fee Goal Date		December 28, 2006
❖ Action Goal Date (if different)		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 		<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (specify type and date for each action taken) 		<input type="checkbox"/> None NA (August 7, 2002)
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3S NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> • Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) • OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

Exclusivity	
<ul style="list-style-type: none"> NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> NDA/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> NDA: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) NDA: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) NDA: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

<p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p>	
<p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p>	
<p><i>If "No," continue with question (3).</i></p>	
<p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p><i>If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p>	
<p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p>	
<p><i>If "No," continue with question (5).</i></p>	
<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or</p>	

<p>its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	December 7, 2006
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	October 25, 2006
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	June 28, 2006
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	October 25, 2006
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 28, 2006
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	October 25, 2006

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> DMETS November 30, 2006 <input checked="" type="checkbox"/> DSRCS September 27, 2006 <input checked="" type="checkbox"/> DDMAC October 26, 2006 & November 2, 2006 <input type="checkbox"/> SEALD N/A <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	July 28, 2006
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	See "Outgoing Correspondence" section
❖ Internal memoranda, telecons, email, etc.	See "Meeting Minutes" section
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> No mtg June 6, 2000 <input checked="" type="checkbox"/> No mtg See "Meeting Minutes" section
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	<input checked="" type="checkbox"/> No AC meeting
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	July 30, 2002, May 29, 1998
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	July 30, 2002

<ul style="list-style-type: none"> • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	February 27, 2002 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: August 29, 2006 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested (August 7, 20010) <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	July 12, 2002, July 17, 1998
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
✓ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested

❖ Clinical review(s) <i>(indicate date for each review)</i>	December 6, 2006, August 5, 2002
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None May 22, 2002 (DDDDP)
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	July 19, 2002, July 8, 2002, March 5, 2002
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	October 23, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested
• Clinical Studies	July 8, 20002
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 8, 2006, July 31, 2002
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 13, 2006, August 1, 2002, August 17, 1998

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-947	Efficacy Supplement Type SE-	Supplement Number
Drug: Pennsaid Topical 1.5% Lotion		Applicant: Dimethaid International
RPM: Nancy Halonen	HFD-550	Phone # 827-2019
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		August 8 2002
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Pediatric waiver 12-3-01
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
General Information	
❖ Actions	
• Proposed action	() AP () TA () AE (x) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	original label of 8-7-01
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	Original 8-7-01
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	8/2/02
❖ Memoranda and Telecons	8/2/02
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	6-5-00
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	8-02-02

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	MTL-8-1-02
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	MO-8-1-02, Derm.5-16-02, AERs review-7-19-02
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	2-13-02
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	7-8-02
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Waiver request 12-3-01
❖ Demographic Worksheet <i>(NME approvals only)</i>	NA
❖ Statistical review(s) <i>(indicate date for each review)</i>	7-31-02
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	8-1-02
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	7-8-02
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	7-29-02
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	Requested 8-7-01
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	
❖ Facilities inspection (provide EER report)	Date completed:7-8-02 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	7-12-02
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	

7/2/02

December 6, 2002

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/s/

Nancy Halonen
12/6/02 11:28:54 AM
CSO

Nancy Halonen
12/6/02 11:32:47 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 19, 2002
TIME: 12:00
LOCATION: Teleconference
APPLICATION: NDA# 20-947 Pennsaid Topical 1.5%
TYPE OF MEETING: Teleconference to discuss clinical trial development.

MEETING CHAIR: Lee S. Simon, M.D.
MEETING RECORDER: Nancy M. Halonen

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division / Name/ HFD#</u>
Lee S. Simon, M.D.	Division Director	FDA/DAAOOP/HFD-550
Larry Goldkind, M.D.	Deputy Director	FDA/DAAOOP/HFD-550
James Witter, M.D., Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
Tatiana Oussava, M.D.	Medical Reviewer	FDA/DAAOOP/HFD-550
Michael Yao, M.D.	Medical Reviewer	FDA/DAAOOP/HFD-550
Suktae Choi, Ph.D.	Statistical Reviewer	FDA/DAAOOP/HFD-550
Carmen Debellas, R.Ph.	Chief Project Manager	FDA/DAAOOP/HFD-550
Nancy Halonen	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Rebecca Keeler	President and CEO	Dimethaid
2. Dr. Zev Shainhouse	Medical Director	Dimethaid
3. Dr. Judith Burgess	Assoc. Medical Director	Dimethaid

Meeting Objectives:

To continue discussion of clinical design issues with Pennsaid and to address the Sponsor comments submitted on November 7 and 14, 2002.

Discussion Points:

- The Division considers DMSO at — to be possibly an active ingredient in Pennsaid both from the standpoint of safety and efficacy, thus, creating a combination product. b(4)
- The Division commented on the poor design of previous trials and the fact that the NDA was difficult to review.
- The Division recognizes the problem with recruitment for a trial of only one knee, but future trials must show a clear efficacy result for each knee treated.
- Please refer to the Division's Advice letter dated October 18, 2002 for the general design of a phase 3 trial to establish the safety and efficacy of both Pennsaid and — DMSO. b(4)
- The sponsor was reminded that the protocol for RA-CP-109 was not discussed with the Division, nor submitted to the IND. The Sponsor was reminded that no lab values were collected in study 109 or 109-US to establish the safety of the DMSO "vehicle" and Pennsaid.
- To address the Sponsor's concern that treating one knee in a clinical trial may be problematic, the Division responded that the Sponsor's statistician should have a separate teleconference with the Division statistician to develop a strategy to adequately address the concerns of data collection with one or two knee treatment.
- The Division reiterated that safety issues are approval issues.
- There will be no change in the Division's opinion on regulatory decisions regarding the non-approval of this NDA.
- The Division stated that the Sponsor could choose one of three options to move forward in the development of this NDA:
 1. Create an alternate trial design to achieve the goals set forth by the Division.
 2. Accept the Division's trial design and carry it out.
 3. Appeal the Division's decision.

Minutes Preparer: Nancy Halonen, Project Manager

Chair Concurrence: Lee S. Simon, M.D., Division Director

cc: Original

HFD-550 Div. Files

HFD550/Meeting Minutes files

HFD-550/RPM

HFD-550/Reviewers & Attendees

Drafted by: nh,

Initialed by:jw,to,ls

final:jw

MEETING MINUTES

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/s/

Lee Simon
11/25/02 06:31:00 PM



NDA 20-947
Dimethaid Research, Inc.
Attention: Eveline Eilert, B.Sc.
Manager, Regulatory Affairs
1405 Denison Street
Markham, Ontario L3R5V2
Canada

Dear Ms Eilert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pennsaid (diclofenac sodium) 1.5% topical lotion. We also refer to your September 24, 2002, containing a statistical analysis plan for clinical study RA-CP-110.

We have reviewed the referenced material and have the following comments and recommendations.

- The Division recommends a study with 6 arms as follow:

	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 oral diclofenac should be 50 mg TID or 75 mg BID with placebo tablets to result in QID dosing to match that of the topical.
- The Division does not agree to a non-inferiority comparison, this study needs to demonstrate superiority to placebo.
- Only one knee (i.e. the target knee) should be treated.
- Use of rescue (acetaminophen) needs to be pre-specified in terms of dose and number of days allowed.
- Only qualified subjects who satisfy all major entry criteria should be randomized. Therefore, all the randomized patients who took at least one study medication should be included in ITT.
- The primary efficacy analysis should be based on the ITT instead of per protocol population.

- The primary efficacy variables (i.e. WOMAC pain and function, patient global assessment) in this 12-week study need to be obtained at baseline, end of study, and at least two more times during the study. Efficacy analyses must address both a landmark analysis at the end of the study and a time-weighted-average analysis during the study. These statistical analyses/models must be pre-specified in the protocol.
- For handling missing efficacy data (5.3.2), imputation according to the WOMAC Users Guide is recommended.
- The Division is open to continued discussion of clinical development plans and offers a teleconference in the near future to offer further guidance.

If you have any questions, call Nancy Halonen, Project Manager, at 301-827-2040.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, M.D.
Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lee Simon

11/5/02 07:10:24 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 10, 2002

TIME: 12:00 EDT

LOCATION: S300

APPLICATION: NDA 20-947 (Pennsaid Topical 1.5% Lotion)

TYPE OF MEETING: Type B Sponsor

MEETING CHAIR: Dr. Lee S. Simon

MEETING RECORDER: Nancy M.Halonen, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division / Name/ HFD#</u>
Lee S. Simon, M.D.	Director	FDA/DAAOOP/HFD-550
Lawrence Goldkind, M.D.	Deputy Director	FDA/DAAOOP/HFD-550
James Witter, M.D.,Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
Stan Lin, Ph.D.	Statistical Team Leader	FDA/DAAOOP/HFD-550
Dennis Bashaw, PharmD	Biopharmacology Team Leader	FDA/DAAOOP/HFD-550
Suktae Choi, Ph.D.	Statistical Reviewer	
Carmen Debellas, R.Ph.	Chief Project Manager	FDA/DAAOOP/HFD-550
Nancy Halonen, BSN,CDE	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
Rebecca Keeler	President & CEO	Dimethaid International Inc.
J. Zev Shainhouse	Medical Director	Dimethaid International Inc.
Judith Burgess	Director, Research & Development	Dimethaid International Inc.

Background:

Dimethaid International Inc. has previously submitted a New Drug Application for review to the FDA. The NDA was found not approvable.

Meeting Objectives:

The Sponsor wishes to discuss the Agency's review to date and the Agency's requirements for approval.

Discussion Points:

- Utilizing tables from the NDA review, members of the Division highlighted what led to the decision for a non-approval.
- The Division stated that the extent of compassionate contralateral use of Pennsaid that was employed in the pivotal studies comprised the bulk of the study and rendered the Division unable to make any conclusions about efficacy for the treatment of a single knee.
- The Division discussed safety issues and stressed that there was a concern of under reporting of any side effects. All three clinical reviewers identified this issue. In addition, there was no meaningful lab data beyond one month in the entire database. Although there has been wide exposure to DMSO previously, controlled safety study with chronic exposure at levels anticipated with Pennsaid use for OA is inadequate.
- The Division commented on the absence of lab data in the two pivotal trials. The Division advised that adequate laboratory monitoring be included in future studies.
- Based on the data submitted in the NDA, the Division expressed concern over the assumption that DMSO is an inactive agent. The Division stated that Pennsaid may be a combination product and suggested the Sponsor consider this concept in development of the next clinical trial design as a step towards approval.
- The Sponsor stated that they now understood the Division's thinking that DMSO may have systemic effects.
- The Division stated that an ongoing non-inferiority trial (with only an active oral comparator) is not adequate to support a future approval.
- The Division offered a trial design for the Sponsor to consider consisting of 4 arms including use of oral agents which could reduce the likelihood of under reporting of adverse events.
- The Division stressed that the future trials must contribute to an adequate safety database before approval.
- The Division advised the Sponsor to maintain continued dialogue with the agency to avoid misinterpreting guidance.

Decisions Reached:

- The Sponsor and the Division will continue dialogue regarding the design of future trials.

Post Meeting Additional Comment:

- Ophthalmologic exams should be considered in future studies in view of previous pre-clinical studies suggesting ophthalmologic toxicity of DMSO.

Minutes Preparer: Nancy Halonen, CSO

Chair Concurrence: Dr. Lee S. Simon

cc: Original

HFD-550/Div. Files

HFD-550/Meeting Minutes files

HFD-550/RPM

HFD-550/Reviewers & Attendees

Drafted bynh 6-4-02

Initialed by: jw, lg 9-19-02

MEETING MINUTES

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/s/

Lee Simon

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MEMORANDUM OF TELECON

DATE: August 15 2002

APPLICATION NUMBER: NDA 20-947 (Pennsaid 1.5% Topical Lotion)

BETWEEN:

Name: Dr. Judith Burgess, Director, Research & Development
Rebecca Keeler, President and CEO
Dr. Zev Shainhouse, Medical Director
Phone: 905-415-1446
Representing: Dimethaid International Inc.

AND

Name: Dr. Dennis Bashaw, Team Leader, Biopharmaceutics
Carmen DeBellis, R.Ph., Chief, Project Management
Nancy Halonen, B.S.N., C.D.E., Project Manager
Representing the FDA, Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

SUBJECT:

The meeting had been requested by the Sponsor to discuss some pharmacokinetics issues relevant to the Non-Approval action taken on 7-Aug-02.

Dr. Bashaw informed the Sponsor that the Division had problems with the assay of the DMSO component of the product. He stated that the Division had adequate information on diclofenac from a pharmacokinetic standpoint. He explained that DMSO is the component of concern citing that single point measurement of DMSO at baseline and at the end of 12 weeks is not adequate to substantiate the degree of absorption of DMSO. There has been no attempt by the sponsor to profile the effects of DMSO.

Dr. Bashaw stated that to meet biopharmaceutical requirements, the sponsor would need a study with a strategy inclusive of a sampling profile at baseline, 1 hour, 2 hour, 4 hour, and at 6 hours after exposure. The profile would need to be of a duration so that if a problem existed, it would be evidenced.

The Sponsor and Dr. Bashaw then discussed a PK study design. Dr. Bashaw reminded the sponsor that bioavailability is a safety issue. The Sponsor was encouraged to design a study of at least one week duration at steady state, focusing on two knee treatment to achieve maximum dosage information (consistent with dermatology designs) with a sample size of 12-16 patients.

The sponsor questioned a tid vs qid regimen with the same amount of total daily dose. Dr. Bashaw advised the Sponsor to design the study to be reflective of their proposed labeling. That is, if the label dosing frequency will be qid, then the study dosing frequency should also be qid.

Dr. Bashaw stated that the review of study 106 especially had problems with a reasonable level of quantification. There was criticism of analytical validation reports. Dr. Bashaw suggested reviewing the FDA guidance on analytical methodology. Dr. Bashaw also wanted to be sure the Sponsor allowed an adequate time to obtain steady-state data.

1 NDA 20-947 (Pennsaid 1.5% Topical Lotion)

The Sponsor questioned the need to sequester patients in the clinic. Dr. Bashaw advised the Sponsor that whatever previous behavior patterns had shown should govern sequestering of patients. If they had been trustworthy previously, they could be let go after the first day sampling.

Because of the existence of DMSO in some foods, Dr. Bashaw advised cautioning patients to continue their regular diets during the study period.

Dr. Bashaw reiterated the Divisions concern about systemic versus local action needing to be substantiated. He advised that between the skin and the site of action, unlike dermatology, is the circulatory system. The question is how much DMSO is diverted by the bloodstream to get to the site of action. For truly topical products, such as a treatment for tinea corporis, by the time the product reaches the capillaries, the product has gone through the site of action. The Sponsor needs additional work in this area to prove a localized action versus a systemic one. Dr. Bashaw suggested the option of microdialysis technique to help in providing the knowledge necessary in this area.

The Sponsor stated they were able to go on with the planned PK issue resolutions.

Nancy Halonen, Project Manager

cc:

Archival IND ———
HFD-550/Division Files
HFD-550/Pharm/Tox Review Team
Drafted by: NH/8-2-02
Initialed by: EDB
Filename:

b(4)

TELECON

2 NDA 20-947 (Pennsaid 1.5% Topical Lotion)

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/s/

Lee Simon

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 29th, 2002

TIME: 12:00 EDT

LOCATION: S300

APPLICATION: NDA 20-947 (Pennsaid 1.5% Topical Lotion)

TYPE OF MEETING: Teleconference

MEETING CHAIR: Dr. Lee Simon

MEETING RECORDER: Nancy M.Halonen, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division / Name/ HFD#</u>
1. Lee S. Simon, M.D.	Division Director	FDA/DAAOOP/HFD-550
2. Lawrence Goldkind, M.D.	Deputy Division Director	FDA/DAAOOP/HFD-550
3. James Witter, M.D., Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
4. Tatiana Oussava, M.D.	Medical Reviewer	FDA/DAAOOP/HFD-550
5. Dennis Bashaw, PharmD	BioPharm Team Leader	FDA/DAAOOP/HFD-550
5. Suktae Choi, Ph.D.	Statistical Reviewer	FDA/DAAOOP/HFD-550
6. Hamid Amouzadeh, Ph.D.	Pharm/Tox Reviewer	FDA/DAAOOP/HFD-550
7. John Smith, Ph.D.	Chemistry Team Leader	FDA/DAAOOP/HFD-550
6. Carmen Debellas, R.Ph.	Chief Project Manager	FDA/DAAOOP/HFD-550
7. Nancy Halonen	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Rebecca Keeler	President and CEO	Dimethaid HealthCare, LTD
2. Dr.Zev Shainhouse, M.D.	Medical Director	Dimethaid HealthCare, LTD
3. Dr. Judith Burgess, M.D.	Associate Medical Director	Dimethaid HealthCare, LTD
4. George E. Markus, M.Sc.	Director, Regulatory Affairs	Dimethaid HealthCare, LTD
5. Eveline Eilert, B.Sc.	Manager, Regulatory Affairs	Dimethaid HealthCare, LTD

BACKGROUND:

This meeting was requested by the sponsor to assist us in our review of the NDA.

Discussion Points and Decisions Reached:

- Dr. Simon conveyed to the sponsor that the review process of this NDA is not yet done and the Division is in the midst of evaluating the data. He reminded the sponsor of the Division review rules which state that once an application has been submitted, no data will be reanalyzed unless the Division requests such reanalysis.
- Dr. Simon then commented on the MCID Analysis approach, acknowledging that it is a valuable tool, but having no role in our discussion today about the Pennsaid review.
- Dr. Simon reiterated that at present, the Division has no idea if the Pennsaid product is approvable.
- The sponsor then offered any help they could give to aid in the Division's review and the Division requested that Trial 105 as well as every patient CRF for trials 109 and 109 US be submitted electronically with hyperlinks or bookmarks to make review easier. The sponsor agreed to this request.
- Dr. Witter also commented that the sponsor should expect to receive other information requests from the Division so as not to miss important elements in making a final decision about this NDA.
- The sponsor had no further concerns and the meeting was adjourned.

Minutes Preparer: Nancy Halonen, CSO

Chair Concurrence: Dr. Lee S. Simon

cc: Original

HFD-550/Div. Files

HFD-550/Meeting Minutes files

HFD-550/RPM

HFD-550/Reviewers & Attendees

Drafted by nh 5-30-02

Initialed by: ls

final:

MEETING MINUTES

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Lee Simon

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- ***** - 301 827 2531- *****

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
 Center for Drug Evaluation and Research, HFD-550
 Parklawn Building
 5600 Fishers Lane, Rockville, MD 20857



To: Ms. Eveline Eilert

From: Ms. Nancy M. Halonen

Fax: 905-415-0827

Fax: 301-827-2531

Phone: 905-415-1446

Phone: 301-827-2019

Pages: (1)

Date: July 23, 2002

Re: NDA 20-947 (Pennsaid Topical 1.5% Lotion) Clinical questions.

Urgent
 For Review Only
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 PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

Hello Eveline,

Our medical reviewer requests the following clinical information. Thank you for your attention to this request.

Please provide the list of deaths, serious adverse events and withdrawals due to adverse events with descriptive summaries for Control-DMSO groups and Placebo groups for each study.

The reviewers have only found tables with rates and require more information as stated above.

Regards,

Nancy Halonen.

MODE = MEMORY TRANSMISSION

START=JUL-08 07:28

END=JUL-08 07:29

FILE NO. = 232

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***** - 301 827 2531- *****

rk
 Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
 Center for Drug Evaluation and Research, HFD-550
 Parklawn Building
 5600 Fishers Lane, Rockville, MD 20857



To: Ms Eveline Eilert

From: Ms. Nancy M. Halonen

Fax: 905-415-0827

Fax: 301-827-2531

Phone: 905-415-1446

Phone: 301-827-2040

Pages: (1)

Date: July 8, 2002

Re: Questions concerning Pennsaid Topical 1.5%

Urgent For Review Please Comment Please Reply Please Recycle

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 PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

Hello Eveline,

Our medical reviewer requests the following clinical information. Thank you for your attention to this request.

Regards,

Nancy Halonen.

1. When was the last patient treated with Pennsaid? Are any patients being treated at the present time?
2. Please summarize, by treatment assignment in study 109 and 109-US, the use of rescue acetaminophen and any other analgesic and/or anti-inflammatory agent (either prescription or over-the-counter) that occurred during these trials.
3. In trial 102-93-1, was a single knee treated throughout the trial?

DSI CONSULT: Request for Clinical Inspections

Date: March 18, 2002

To: Jose Carreras, GCPB Reviewer/HFD-47

Through: Martin H. Cohen, M.D., Acting Director, DSI, HFD-45
Lee S. Simon, M.D., Director, HFD-550

From: Nancy Halonen, Project Manager, HFD-550

Subject: Request for Clinical Inspections
NDA 20-947
Dimethaid Research, Inc.
Pennsaid (difloclofenac sodium) lotion

Protocol/Site Identification:

Please contact George Markus, Director of Regulatory Affairs for site addresses: 905-415-1446. Extension 230. Per Dr. Witter, the sites with the highest enrollment would be the most valuable for investigation. These sites were not found in the original drug application, Vol. 1.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
------------	------------	-------------------------	--------------------

No sites listed			
-----------------	--	--	--

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

There are insufficient domestic data

- Only foreign data are submitted to support an application**
- Domestic and foreign data show conflicting results pertinent to decision-making**
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.**
- Other: Canadian Study RA-CP-109 protocols were not discussed, nor submitted with the IND**

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **May 20, 2002**. We intend to issue an action letter on this application by (action goal date) **June 7, 2002**.

Should you require any additional information, please contact Nancy Halonen. 301-827-2019.

Concurrence: (if necessary)

James Witter, Medical Team Leader
James Witter, Medical Reviewer

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/s/

Nancy Halonen
4/15/02 12:26:37 PM



NDA 20-947

Dimethaid Research, Inc.
Attention: George Markus, M.Sc.
Director, regulatory Affairs
1405 Denison Street
Markham, Ontario L3R5V2
Canada

Dear Mr. Markus:

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

On March 29, 2002, we received your March 28, 2002 electronic submission. This would be considered a major amendment to this application. The receipt date is within 3 months of the primary user fee goal date, allowing extension of the goal date by three months to provide time for a full review of the submission. The extended primary user fee goal date is September 8, 2002. The secondary user fee goal is November 8, 2002.

If you have any questions, call Nancy Halonen, Project Manager, at 301-827-2040.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
4/9/02 03:42:24 PM

MODE = MEMORY TRANSMISSION

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END=APR-03 10:09

FILE NO. 176

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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-FDA CDER ODEV DAAD HFD550-

- ***** -

301 827 2531- *****

Fx
Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



To: George Markus

From: Ms. Nancy M. Halonen

Fax: 905-415-0827

Fax: 301-827-2531

Phone: 905-415-1446

Phone: 301-827-2019

Pages: (1)

Date: April 3, 2002

Re: Clinical Reviewer Request for NDA 20-947, Pennsaid Topical Solution

Urgent For Review Please Comment Please Reply Please Recycle

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Hello George,

Our medical reviewer requests the following clinical information:

1. Please supply a list of those patients in protocol 109 and 109US that had both knees treated at any point in the trial and indicate which knee was the target knee in these patients.
2. Please list, at baseline and end of study, the target knee and treated knee for each patient in protocols 109 and 109US.
3. Please indicate how the original data from the study site on WOMAC endpoints and patient global were entered into the database in these two studies.

Thank you for your attention to this request. Regards, Nancy Halonen

Fax
Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug
Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



To: George Markus

From: Ms. Nancy M. Halonen

Fax: 905-415-0827

Fax: 301-827-2531

Phone: 905-415-1446

Phone: 301-827-2019

Pages: (1)

Date: March 28, 2002

Re: Clinical Reviewer Request for NDA 20-947, Pennsaid Topical Solution

Urgent For Review Please Comment Please Reply Please Recycle

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ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND
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Hello George,

Our medical reviewer requests the following clinical information:

- 1. Who in protocol 109 Canada, and 109 US had both knees treated.**
- 2. How were the data entered from the principle investigators in these trials.**

Thank you for your attention to this request. Regards, Nancy Halonen

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/s/

Nancy Halonen
3/28/02 11:04:40 AM
CSO

Fax
Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug
Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



To: George Markus

From: Ms. Nancy M. Halonen

Fax: 905-415-0827

Fax: 301-827-2531

Phone: 905-415-1446

Phone: 301-827-2019

Pages: (4)

Date: March 21, 2002

Re: Clinical Reviewer Request

Urgent For Review Please Comment Please Reply Please Recycle

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ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND
PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

Hello again George,

Our chemistry reviewer requests the following clinical data. Thank you for your attention to this request.
Regards, Nancy Halonen

NDA 20-947, Pennsaid Topical Solution
List of Chemistry Deficiencies and Comments

1. The following comments pertain to the drug product specification:
 - (a) Identification tests should be specific for the drug substance. Identification solely by the retention time of the major peaks in the HPLC chromatogram is not adequate. If the ID test is not specific, two identification tests should be provided. Please refer to ICH Q6A, Section 3.2.2 (b).
 - (b) The acceptance criteria for each individual unknown impurity _____ is not justified by the stability data. The stability results presented in volume 3, pages 70-138 show unknown impurities at levels _____ before expiry for some batches.
 - (c) You have changed the lower acceptance limit of ethanol from _____ to allow for losses during shelf life. Your investigation report (volume 3, pages 180-182) indicates

b(4)

-
- (d) Clarify the analytical method used for dimethyl sulfoxide assay. The analytical method described in the method section (volume 2, page 97 and 155) indicates that GC is used for the dimethyl sulfoxide assay. However, the specification page (volume 2, page 86) shows that it is HPLC. **b(4)**
2. The storage temperature (between 4°C and 10°C) and the solution head space _____ should be specified in the manufacturing procedure for the storage of bulk solution between end of manufacturing and beginning of filling, since the stability of the bulk solution was based on the data obtained from the study performed under these conditions.
3. The following comments pertain to the stability data of the drug product:
- (a) The 8/7/01 submission shows that several lots of the drug product stored under 25 °C/60%RH failed the acceptance criteria for individual unknown impurities at 24 months. However, the 2/13/02 amendment shows that they meet the criteria after re-analysis by _____. Please provide scientific rationale for disregarding the data in the 8/7/01 submission. **b(4)**
- (b) Concerning the color change from “colorless to pink” to “orange”, the color-forming compounds should be identified and qualified. Your method for degradation products is not validated to be able to detect the color-forming compounds.
- (c) Please provide deviation reports for your stability data.
4. Your post-approval stability protocol indicates that the drug product will be stored at 25°C (15-30°C range) and ambient humidity. It is requested that the product be stored under 25°C ± 2°C/40% RH ± 5% RH for the long-term stability study in accordance with section II.7.c. of ICH Q1A (R) (August 2001 revision) for drug products packaged in semipermeable containers.
5. An extension of the expiration dating period should be based on full long-term stability data.
6. The following deficiencies were found in the methods validation packages:
- (a) Please revise drug product specification section as stated in comment #1 above.
- (b) Please follow FDA “Guideline for Submitting Samples and Analytical Data for Methods Validation.” Your method validation package is deficient as follows:
- The table of samples should include samples of impurities reference standards
 - Statement of composition of finished dosage forms
 - Material safety data sheets (MSDS) for the drug substance and drug product.
7. The following comments pertain to the labeling:
- (a) It is incorrect that the bottle and carton labeling state that “each gram of the solution contains 16.05 mg diclofenac sodium”. Your drug product information indicates that _____ **b(4)**
_____ In addition, it is recommended that the content

March 21, 2002

be expressed as "weight in volume" for a liquid preparation (21 CFR 201.10 (d)(2)), e.g. each mL contains x mg of active.

- (b) The expiration date and lot number should appear on the immediate container and also the outer package, in accordance with 21 CFR 201.17.
- (c) The alcohol content should be stated in accordance with FD&C Act 502.(e).1.(ii) and 21 CFR 201.10.(d)(2).
- (d) In the Description section, right before the structure, "diclofenac" should be changed to "diclofenac sodium". Acetonitrile was incorrectly spelled.
- (e) For safety reason, it is recommended that "for external use only" be displayed on all the labels.

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/s/

Nancy Halonen
3/21/02 01:26:28 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 11, 2002
TIME: 14:00
LOCATION: Teleconference
APPLICATION: NDA# 20-947 Pennsaid Topical 1.5%
TYPE OF MEETING: Teleconference to discuss labeling.

MEETING CHAIR: James Witter, M.D., Ph.D.
MEETING RECORDER: Nancy M. Halonen

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division / Name/ HFD#</u>
1. Lee S. Simon, M.D.	Division Director	FDA/DAAOOP/HFD-550
2. James Witter, M.D., Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
3. John Smith, Ph.D.	Chemistry Team Leader	FDA/DAAOOP/HFD-550
4. Hamid Amouzadeh, Ph.D.	Pharmacology Reviewer	FDA/DAAOOP/HFD-550
5. Carmen Debellas, R.Ph.	Chief Project Manager	FDA/DAAOOP/HFD-550
6. Nancy Halonen	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Rebecca Keeler	President and CEO	Dimethaid
2. Dr. Zev Shainhouse	Medical Director	Dimethaid
3. Dr. Judith Burgess	Assoc. Medical Director	Dimethaid
4. Jagat Singh	Supervisor, Research&	Dimethaid

	Development	
5. George E. Markus, M. Sc.	Director, Regulatory Affairs	Dimethaid
6. Kate Williams	Manager, Clinical research	Dimethaid
7. Eveline Eilert	Manager, Regulatory Affairs	Dimethaid
8. Michelle Hershoran	Senior Associate, Regulatory Affairs	Dimethaid

b(4)

Meeting Objectives:

1. To discuss Division concerns with labeling.
2. To discuss Division concerns with the NDA application.

Discussion Points:

The Division wished to convey and clarify the following regarding labeling :

1. The Division considers DMSO to be an active ingredient. The labeling should reflect this as far as toxicity and carcinogenicity are concerned.
2. The labeling needs to be revised to include the NSAID template in all components (including the GI warning component).
3. In order to remove the GI paragraph as noted in #2 above, any sponsor must demonstrate (with replicated endoscopic studies and large patient outcome trials) that such removal would be appropriate product labeling.
4. Any labeling language will include " only for knees" as the _____ Product labeling may also note this could only be an adjunct to other therapies, not a stand- alone product.

b(4)

The Division wished to convey the following regarding the NDA application:

1. Review of this NDA application has been hampered by the generally poor quality of the submission.
2. The sponsor was reminded that protocol for RA-CP-109 was not discussed with the Division, nor submitted to the IND.
3. The sponsor will be receiving a fax from the Chemistry soon.

DECISIONS (AGREEMENTS) REACHED:

1. George Markus will send the Division a hard copy of the main submission with hyper-links to assist with the review.

Minutes Preparer: Nancy Halonen, Project Manager

Chair Concurrence: James Witter, M.D., Ph.D

cc: Original

HFD-550 Div. Files

HFD550/Meeting Minutes files

HFD-550/RPM

HFD-550/Reviewers & Attendees

Drafted by: nh,

Initialed by: jw

final: jw 3/19/02

MEETING MINUTES

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/s/

Lee Simon

3/19/02 04:17:05 PM

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***** - 301 827 2531- *****

Fig
 Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug
 Products
 Center for Drug Evaluation and Research, HFD-550
 Parklawn Building
 5600 Fishers Lane, Rockville, MD 20857



To: George Markus

From: Ms. Nancy M. Halonen

Fax: 905-415-0827

Fax: 301-827-2531

Phone: 905-415-1446

Phone: 301-827-2019

Pagcs: (1)

Date: March 19, 2002

Re: Clinical Reviewer Request

Urgent For Review Please Comment Please Reply Please Recycle

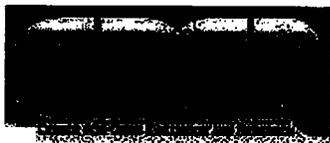
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Hello again George,

Our medical reviewer requests the following clinical data. Thank you for your attention to this request.
 Regards, Nancy Halonen

NDA 20-947, Pennsaid Topical 1.5% lotion

This request pertains to both the US and Canadian 109 studies. Which patients (with I.D. numbers) received treatment to both knees in protocol 109 and 109 US? If this information is in what has already been submitted, please give us the exact location to find it.



MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: 4 November 2003

TIME: 10:00 am – 11:00 pm (EST)

LOCATION: 9201 Corporate Blvd, HFD-550, S-300 (site of teleconference)

APPLICATION (DRUG): NDA 20-947/IND 42,773, Serial #48 (PENNSAID® 1.5% Topical Solution)

SPONSOR: Dimethaid International, Inc.

TYPE OF MEETING: Sponsor requested feedback on the proposed revised Protocol #PEN-03-112

MEETING CHAIR: Lee Simon, MD

MEETING RECORDER: Paul Z. Balcer

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Lee S. Simon, MD	Division Director	ODEV/DAAODP, HFD-550
2. James Witter, M.D., PhD	Medical Team Leader	ODEV/DAAODP, HFD-550
3. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
4. Stan Lin, PhD	Statistics Team Leader	ODEV/DAAODP, HFD-550
5. Suktae Choi, PhD	Biostatistics Reviewer	ODEV/DAAODP, HFD-550
6. Carmen DeBellis, RhP	Chief Project Manager	ODE V/DAAODP, HFD-550
7. Paul Z. Balcer	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Zev Shainhouse, MD	Medical Director	Dimethaid Research, Inc.
2. Rebecca Keeler	President & CEO	Dimethaid Research, Inc.
3. Judith Burgess	Director, Research and Development	Dimethaid Research, Inc.
4. Mimi Brennan	Director, Regulatory Affairs	Dimethaid Research, Inc.

PURPOSE OF THE MEETING: To obtain guidance on the proposed revised protocol PEN-03-112.

MEETING OBJECTIVES: To obtain Division's feedback on the proposed protocol and accompanying questions from the Sponsor.

QUESTIONS:

Question 1: Are the proposed changes/responses acceptable to the FDA?

Initial FDA Response:

Yes, with the additional suggestions:

To include patient weight under Demographic and Baseline variable (6.2) because it is important independent risk factor for osteoarthritis.

To include Bilirubin into laboratory testing and define what values would constitute a clinically significant laboratory abnormality.

To use Patient Overall Health Assessment as a primary end-point, and Patient Global Assessment of the study knee as a secondary end-point.

To do evaluations at 0-4-8-12 weeks instead of 0-2-6-12 as proposed by the Sponsor; equal intervals between evaluations would facilitate comparison of data between intervals.

To include an analysis of WOMAC pain by a time-weighted-average approach as a secondary endpoint with the weighting toward the end of the trial. These weighted results need to be consistent with the treatment effect noted in the primary outcome.

The ITT group must include all the patients who are randomized and take any medication. You can not exclude any subjects from ITT after randomization. Therefore, the definition of ALL in page 30 is the definition of ITT.

Meeting comments:

Patient Global Assessment should look at the patient's overall experience with the drug.

Question 2: Once finalized and approved, this clinical study should meet all outstanding issues relating to the efficacy and safety of the product, and will form the primary basis for the marketing approval of PENNSAID® Topical Solution, 1.5% w/w diclofenac sodium, NDA 20-947. Does the FDA agree, assuming that the study will be successful and will meet the study objectives?

Initial FDA Response:

Approval will be based on the results of the review of this study, along with data from the prior NDA submission.

Meeting comments:

Approval of the drug will be based on the totality of the new evidence in addition to the past evidence submitted to the Division.

Sponsor's pivotal study should show an improvement in the target knee.

Question 3: What kind of labeling statements could be expected if the data are supportive and the product is approved?

Initial FDA Response:

Although any final label will be a review issue, the Sponsor should expect to have an indication for the treatment of the signs and symptoms of the OA of the knee only. It is expected that the label will contain language in line with the NSAID template.

Minutes Preparer: Paul Z. Balcer
Chair Concurrence: Brian E. Harvey, MD, PhD, Acting Division Director
Drafted by: PZBalcer
Initialed by: BEHarvey
Final: 1/16/04

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/s/

Brian Harvey
1/16/04 04:01:25 PM

Carmen DeBellas
1/21/04 09:44:08 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 29, 2002
TIME: 13:00 EDT
LOCATION: S300
APPLICATION: IND 42,773/NDA 20-947 (Pennsaid 1.5% Topical Lotion)
TYPE OF MEETING: Teleconference
MEETING CHAIR: Dr. Lee Simon
MEETING RECORDER: Nancy M.Halonen, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division / Name/ HFD#</u>
Lee S. Simon, M.D.	Division Director	FDA/DAAOOP/HFD-550
James Witter, M.D., Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
Dennis Bashaw, PharmD	BioPharm Team Leader	FDA/DAAOOP/HFD-550
Suktae Choi, Ph.D.	Statistical Reviewer	FDA/DAAOOP/HFD-550
Hamid Amouzadeh, Ph.D.	Pharm/Tox Reviewer	FDA/DAAOOP/HFD-550
Stan Lin, Ph.D.	Statistical Team leader	FDA/DAAOOP/HFD-550
Nancy Halonen	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
Rebecca Keeler	President and CEO	Dimethaid HealthCare, LTD
Dr.Zev Shainhouse, M.D.	Medical Director	Dimethaid HealthCare, LTD
Dr. Judith Burgess, M.D.	Associate Medical Director	Dimethaid HealthCare, LTD

BACKGROUND:

The Sponsor seeks Division advisement on their proposed clinical development strategies relative to resubmission of an NDA. After a brief introduction by the Sponsor, the Division proceeded to answer the questions. The Sponsor was provided with draft responses to all questions prior to the teleconference. The answers below include the discussion that the teleconference generated:

Pertaining to proposed study protocol No. PEN-03-112:
"Does the protocol address all of the Division's issues?"

CLINICAL

FDA Response:

- *The Division is concerned about the differing treatment strategy in this protocol (i.e., 50 drops tid) versus the treatment in the original NDA studies (i.e., 40 drops qid). This will make it difficult to synthesize these differing data sets into a comprehensive label with regard to dose and dosing interval. Therefore, the data from this protocol would not be able to be considered with the original NDA data toward approval.*
- *The Division believes that Pennsaid as currently formulated may represent a combination drug product. As a combination drug, each component (in this case diclofenac and DMSO at _____) must demonstrate a clinical contribution to the effect of the combination. The Division also understands that the Sponsor does not view Pennsaid to be a combination drug. Consequently, the statistical analysis plan needs to address both of these possibilities.*
- *The Division considers the change in WOMAC score of at least 10% of scale from the baseline score to represent a minimal clinically important difference for this protocol regardless of the number of patients in each arm.*
- *The proposed definition of a flare is not acceptable since the Division is concerned that this patient population will have insufficient disease activity to see an effect. The Sponsor is recommended to redefine the definition of a flare requiring the patients to be more symptomatic at entry. Please provide your justification for this revised flare definition.*
- *The Division strongly recommends laboratory analysis at week 6. Also, it is unclear why the laboratory testing will not be available until after randomization is completed and the treatment started.*
- *The Division agreed with the Sponsor's justification for this rationale.*
- *It is unclear how the use of acetaminophen will be analyzed in this protocol. It is also unclear when a patient will have failed the protocol due to the use of this rescue. Please clarify both of*

b(4)

these issues. It is important, if not evidence of failure, that some approach to ascertaining the use of the rescue medication is clearly described in the design.

- *The Sponsor will submit a revised protocol defining what happens when someone fails.*
- *Please revise the patient global question. As it currently stands, this is another assessment of efficacy. The patient global needs to assess the patients' experience with the drug (both in terms of efficacy and safety) during the trial.*
- *The Division will work with the Sponsor to create a more appropriate patient global question.*
- *Pregnancy test should be included and pregnant woman should not be allowed into the trial.*
- *It is unclear to the Division how the Sponsor will ensure that the patient will not apply the solution to the "non-target" knee and that it is always the original "target" knee that is constantly evaluated for efficacy.*
- *The Sponsor needs to follow-up patients for at least 1 week after the study completion to catch possible adverse events that may be delayed.*
- *The Sponsor must follow all AEs until resolution.*
- *The Sponsor needs to pre-specify abnormal lab criteria for discontinuation from the study.*

CLINICAL PHARMACOLOGY

FDA Response:

No PK related issues were identified in the protocol. The Sponsor is reminded of our outstanding comments from previous communications relating to a current evaluation of the absorption and metabolic fate of DMSO and its metabolites.

NONCLINICAL PHARMACOLOGY

FDA Response:

There are no nonclinical pharmacology issues identified with this protocol.

CHEMISTRY

FDA Response:

There are no CMC issues.

STATISTICS

FDA Response:

- *In addition to the proposed primary analysis, please provide a statistical comparison of DMSO — (Group 3) vs. DMSO 1/20th (group 4) as part of the secondary analyses*
- *Please include the use of rescue medication into the secondary analyses.*
- *Patients in each treatment arm should be stratified into the number of knees symptomatic with OA. In other words, patients with one knee involved and patients with both knees involved with OA should be randomized separately. All the efficacy analyses should include this stratification.*
- *The ITT group must include all the patients who are randomized and take any medication. The qualification of the subject should be evaluated during the screening period, and unqualified subjects should be excluded from randomization. You can not exclude any subjects from ITT after randomization.*

b(4)

Discussion Points and Decisions Reached:

A statistical teleconference will be scheduled in the future to discuss the Sponsor's new statistical strategies.

The Division reiterated the need to provide extended efficacy data in the study. The Sponsor was encouraged to create a mechanism that captures efficacy once the patient leaves the trial and takes rescue.

The Sponsor will provide the Division with a revised protocol implementing the advisement received in the teleconference.

Minutes Preparer: Nancy Halonen, CSO

Chair Concurrence: Dr. Lee S. Simon

cc: Original

HFD-550/Div. Files

HFD-550/Meeting Minutes files

HFD-550/RPM

HFD-550/Reviewers & Attendees

Drafted by nh 8-29-03

Initialed by:

final:

IND 42,773/NDA 20-947 (Pennsaid Topical 1.5% Solution) Teleconference meeting Minutes of August 29, 2003

Pg. 4

MEETING MINUTES

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/s/

Lee Simon

9/22/03 03:07:34 PM

MEMORANDUM OF TELECON

DATE: January 6, 2003

APPLICATION NUMBER: NDA 20-947 (Pennsiad)

BETWEEN:

Name: Dr. Zev Shainhouse
Rebecca Keeler
Dr. Judith Burgess

Phone: 905-415-1446
Representing: Dimethaid International, Inc.

AND

Dr. Dennis Bashaw, Biopharmaceutical team Leader,
Carmen DeBellis, R.Ph., Chief, Project Management,
Nancy Halonen, B.S.N., C.D.E., Project Manager,
Representing: The Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

SUBJECT:

Discussion about the official method of document submission and the benefits of following the standards.

The Division conveyed to the Sponsor the following:

- All protocols need to be submitted officially, not just as desk copies. This mechanism allows for tracking all the documents in our filing system and prevents loss of documents.
- This system allows for retrieval of archival documents for review and reference in the future.
- If documents are not officially submitted, reviews of the submissions cannot be electronically attached to the documents and reviews may be lost, as well as making it impossible to have them reviewed and signed by Division personnel.
- The Division will give commentary on the officially submitted protocols in a realistic timeframe.
- The Sponsor stated they understood the logic of the submission guidance.

Nancy Halonen, Project Manager
Dr. Dennis Bashaw, BioPharm Team Leader

cc:

Archival IND 42,773/NDA 20-947

HFD-550/Division Files

Drafted by: NH/1-6-03

Initialed by: cd 1-6-03

TELECON

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/s/

Nancy Halonen
1/7/03 07:42:41 AM
CSO

Dennis Bashaw
1/10/03 03:54:49 PM
BIOPHARMACEUTICS



NDA 20-947

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

Dear Dr. Ballantyne:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pennsaid Topical Solution (1.5% diclofenac sodium) solution

Review Priority Classification: Standard (S)

Date of Application: August 07, 2001

Date of Receipt: August 08, 2001

Our Reference Number: NDA 20-947

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 08, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 08, 2002 and the secondary user fee goal date will be August 08, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a

"Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
HFD-550
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Barbara Gould, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Mary Jane Walling
Acting Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic &
Ophthalmic Drug Products
Office of Drug Evaluation 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/

Barbara Gould
9/14/01 01:26:05 PM
Barbara Gould for

MODE = MEMORY TRANSMISSION

START=SEP-12 19:16

END=SEP-12 19:17

FILE NO. = 019

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301 827 2531- *****

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: George Markus	From: Barbara Gould
Fax: 905 415-0827	Fax: 301 827-2531
Phone: 905 415-1446	Phone: 301 827-2019
Pages: 1 (including cover)	Date: 12-Sep-01
Re: NDA 20-947	

Urgent For Review Please Comment Please Reply Please Recycle

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● **Comments:**

Per our conversation on 12-Sep-01, please provide the following information:

- Please refer to the minutes from the meeting held on June 5, 2000. You have indicated that pre-clinical skin sensitivity studies were performed with Pennsaid. Please provide the study reports from these studies.
- In addition, please provide an update on the reproductive toxicity, genotoxicity, dermal toxicity and carcinogenicity of DMSO, i.e. any recent study reports or information, besides those that have been submitted with previous filing of the NDA.
- Please indicate when the results of protocol RA-CP-109-US will be available to the Division for review.
- Please provide statistical data in SAS format for review.
- If possible, please provide on diskettes or CD ROM as a reviewer aid a copy of the NDA in Word 97 format.

Please call if you have any questions.



Food and Drug Administration
Rockville MD 20857

OCT 30 1998

NDA 20-947

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

Dear Dr. Shainhouse:

We acknowledge receipt of your October 26, 1998, correspondence notifying us that you are withdrawing your December 15, 1997, new drug application (NDA) for Pennsaid (diclofenac sodium topical lotion) 1.5% w/w.

Therefore, in accordance with 21 CFR 314.65, this application is withdrawn as of the date of our receipt of your notification, October 30, 1998. This withdrawal does not prejudice any future filing of the application. You may request that the information contained in this withdrawn application be considered in conjunction with any future submission.

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

Sincerely,

J E H 10-30-98

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/VLutwak

HFD-550/MAverbuch/CYaciw/DWang/AWeir

HFD-170/ SLin/BTaneja

HFD-95/DDMS

HFD-105/ADRA

HFD-560/OTC (for OTC applications only)

HFD-324/DMPQ (if there is a pending EER)

HFD-340/DSI (if there is a pending clinical audit)

DISTRICT OFFICE

Drafted by: VL/October 28, 1998

Initialed by:

final:

filename: 981028WD.

WITHDRAWN (WD)

4.4 ENVIRONMENTAL ASSESSMENT

Request for categorical exclusion from the requirement of preparing an Environmental Assessment for approval of NDA 20-947 follows.

Environmental Assessment
21 CFR 25.15

Pursuant to 21 CFR 25.15 (d), Dimethaid International Inc. hereby claims a categorical exclusion from the requirement of preparing an Environmental Assessment for approval of NDA 20-947.

Under Section 25.31 (b), a categorical exclusion exists for:

Action on an NDA, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

Dimethaid International Inc. also certifies that, to the best of its knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)) to prevent categorical exclusion under Section 25.31 (b).

Dated, this 7th day of August, 2001.

DIMETHAID INTERNATIONAL INC.

Per: 
George E. Markus, M.Sc.
Director, Regulatory Affairs

550 y. Kong

MEETING MINUTES

MEETING DATE: June 5, 2000 **TIME:** 2:00 p.m. – 4:00 p.m. **LOCATION:** CORP S 300

IND#: 42,773

Meeting Request Submission Date: April 14, 2000
Meeting Scheduled Date: April 27, 2000
Briefing Document Submission Date: May 17, 2000
Additional preparation documents: May 29, 2000

DRUG: Pennsaid (diclofenac topical lotion) Lotion

APPLICANT: Dimethaid International Inc.

TYPE of MEETING: pre-NDA

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Karen Midthun, M.D.	Division Director, DAAODP
James Witter, M.D., Ph.D.	Medical Reviewer
Abi Adebawale, Ph.D.	Pharmacokinetics Reviewer
Dennis Bashaw, Pharm.D.	Pharmacokinetics Team Leader
Laura Lu, Ph.D.	Statistics Reviewer
Stan Lin, Ph.D.	Statistics Team Leader
Hamid Amouzadeh, Ph.D.	Pharmacology/Toxicology Reviewer
Robert Osterberg, R.Ph., Ph.D.	Acting Pharmacology/Toxicology Team Leader
Sue-Ching Lin, M.S., R.Ph.2.	

Mona Zarifa, Ph.D.	Acting Chemistry Team Leader
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

Rebecca E. Keeler	President and CEO- Dimethaid
Zev Shainhouse, M.D., B.Sc., F.R.C.P.C.	Medical Director- Dimethaid
George E. Markus, M.Sc.	Director, Regulatory Affairs-Dimethaid

MEETING OBJECTIVES: To provide a response to sponsor's questions as detailed in the January 20, 2000, meeting background materials.

b(4)

BACKGROUND INFORMATION: Sponsor requested this meeting to discuss adequacy of existing pre-clinical, clinical, CMC information for submission of new NDA. More specifically, sponsor requested feedback on adequacy of clinical program with regard to proposed critical study (Study #RA-CP-109). Specific items for discussion were provided in meeting background package dated May 17 and 29, 2000 (Serial number 018).

Brief history of IND:

IND 42,773 submitted on June 8, 1993. Partial hold letter issued on September 16, 1993 for CMC and toxicology deficiencies. June 7, 1995- removal of partial hold. Submitted NDA 20-947 on December 15, 1997. Subsequently, application withdrawn by sponsor due to PAI issues on October 3, 1998.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Please confirm that the clinical program as summarized in Attachment #2 is adequate to support the proposed indication.**

FDA Response: FDA does not confirm.

- Study #102-93-1 (osteoarthritis (OA)- knee) and study #108-97 (OA-hand) do not demonstrate efficacy.
- Study 105-95 (open-label study) contributes safety data, not efficacy.
- Study 107-96 (knee- OA study) demonstrates some efficacy. However, as stand alone information, this is not sufficient to support your desired claim.
- Study #RA-CP-109 (a new study being conducted in Canada, not previously submitted to the US IND) by design does not appear likely to provide sufficient evidence. For example, a 6-week study is proposed; but a 12-week study duration is currently preferred for this chronic condition. Also, OA studies should include three standard endpoints [e.g., pain, function (WOMAC), patient global assessment] not just the one primary endpoint proposed in the study protocol.

With regard to study #RA-CP-109, sponsor requested elaboration on FDA response. FDA noted that we currently recommend 12-week studies in the evaluation of topical NSAIDs for the indication of OA. The reason for this is that we have limited experience with topical NSAID preparations, in contrast to oral NSAIDs. Also, per OA draft guidance document, three primary endpoints need to be addressed [e.g., pain, function (WOMAC), patient global assessment] as mentioned earlier.

FDA indicated that these recommendations would have been provided to the sponsor with respect to Study #RA-CP-109, but that this had not been possible due to the fact that this protocol was not submitted to the IND. FDA first became aware of this study when the protocol was submitted on May 17, 2000, as part of the meeting materials for the current meeting. Also, the sponsor verified via our telephone inquiry on May 30, 2000, that this study was a non-US IND study being conducted in Canada. FDA inquired as to whether at our August 25, 1999 sponsor meeting, study #RA-CP-109 was described or introduced to FDA. Sponsor responded that information pertaining to this protocol was not shared with the FDA at that time, but they would provide data when these became available to FDA for informational review.

The sponsor indicated that in follow-up to the August 25, 1999, meeting, they thought that they had a clear understanding of what additional studies would be required and therefore, did not seek further FDA input until the present time. FDA noted that the August 25, 1999, meeting had not been an end-of-phase 2 (EOP2) meeting, and that FDA had recommended at that meeting that the sponsor return for an EOP2 meeting to discuss specific proposals for completion of their clinical development program. The sponsor noted that they had not received the meeting minutes from that meeting. FDA conveyed to sponsor that these would be provided to the sponsor.

With regard to Study #RA-CP-109, the sponsor pointed out that it had been started in Canada in December of 1999. Currently, 170 patients have completed the study with an anticipated total enrollment of 200 patients. Also, sponsor clarified for FDA that the placebo was identical to the carrier for the study drug.

The sponsor informed FDA that they thought this study was adequately powered to allow an evaluation of the three primary endpoints discussed above. Furthermore, they asked if amending the study accordingly would be adequate. FDA responded that there would still be only a 4-week and a 6-week study for assessment of efficacy, and this was problematic in view of the current approach, which involves two 12-week efficacy studies for evaluation of topical products for OA. FDA noted that in light of the duration of ongoing development, a 6-week and a 12-week study could be adequate. The sponsor inquired whether a very high level of efficacy (e.g., a very low p-value) in the ongoing 6-week study would make another study unnecessary. FDA explained that if one can split a study in half and still have significance, that suggests robustness. However, this does not address the need for two separate studies of adequate duration.

The sponsor questioned the feasibility of conducting a 12-week placebo-controlled study. FDA informed sponsor that studies of 12-week duration have been done often for OA products with provisions for rescue medications, usually acetaminophen. FDA, also, recommended including an oral NSAID in such a study as a comparator. The sponsor responded that they were unable to determine what the appropriate oral comparator should

be; they believed that the use of the WOMAC endpoint allowed them to position the product, because the WOMAC was developed with oral diclofenac.

The logistics of conducting another study were discussed. The sponsor indicated that it was more difficult to enroll patients in their studies because of competing studies with other products. They further explained that it was difficult to perform a flare-design study, because approximately 40% of patients would not be eligible. FDA informed sponsor that they could conduct a study with or without a flare design.

The sponsor pointed out that the draft OA guidance at the time prior to and at the August 25, 1999 meeting with FDA, recommended studies of 6-week duration for oral NSAIDs. Also, the sponsor emphasized that study duration period was not previously raised as an issue. FDA responded that different approaches may be developed for oral vs. topical formulations of drug products depending on the previous body of experience. FDA noted that the guidances are not all-inclusive and the draft OA guidance did not specifically address topical NSAID drug products.

FDA reminded sponsor that during the August 25, 1999 meeting, a major topic of discussion was the fact that the hand OA trial failed; at that time, FDA suggested that sponsor submit proposals regarding possibly another ————— knee study. However, there was no discussion relating to specifics of such trial designs. FDA pointed out that if efficacy was demonstrated only for knee OA, then the indication would be limited to knee OA and would accordingly be reflected in the labeling. b(4)

It was agreed that the sponsor would submit to the IND a proposal for revising the ongoing Canadian study (#RA-CP-109) to include the three primary endpoints discussed earlier and an extension of duration of study to 12 weeks.

Sponsor voiced their concern regarding FDA's input turn-around time if indeed they did submit changes to the protocol for FDA review, since the element of time would be crucial to their drug development plan. FDA stated that such a request would be considered as a type A meeting. To further facilitate this, FDA suggested that desk copies be submitted for all appropriate reviewers in addition to formal submission to IND for archive.

As an aid to assist FDA reviewers in considering the design of future studies that may be designed to evaluate the effectiveness of this product, please submit a tabular summary of efficacy data from all completed/ongoing Pennsaid trials to date. For each trial, include the following:

- number of patients
- duration of treatment with Pennsaid and controls
- concise description of controls used in each trial

- primary and secondary endpoints for each treatment group in each trial
 - patient population analyzed (e.g., ITT, per protocol, any variations)
 - statistical results (e.g., p-values, trends, etc.) and methods/tests employed for all primary and secondary endpoints.
2. **With the resubmission, Dimethaid proposes to submit an additional Pivotal Study (Study #RA-CP-109) with efficacy data only. The full Study report would follow shortly thereafter (approx. 4-8 weeks), upon completion of the data processing required for the remainder of the safety data. The support for this position can be justified by the overwhelming set of preexisting safety data that will be included in the main submission (see safety summaries presented in Attachment #2). Concurrence by FDA is respectfully requested. The Integrated Summary of Safety would be updated in the 4-month Safety Update.**

FDA Response: see response to Question #1.

At time of NDA submission, FDA generally expects submission of full study reports for those studies deemed critical to the review of the application. Abbreviated study reports (with full safety data) may be adequate for studies that provided safety data but did not provide information relevant to the evaluation of effectiveness in the proposed indication.

3. **Please confirm that the proposed NDA resubmission Table of Contents is acceptable (see Attachment #4).**

FDA Response: With respect to CMC section, please include the following:

- a. Begin with a list of changes made to the original submission. In addition, on the first page of each CMC subsection, the resubmission should include a list of changes pertinent to that subsection.
- b. The resubmission should contain a response to CMC deficiencies cited in our Deficiencies/Comments letter dated 12/16/98 regarding NDA 20-947. Restate deficiencies, followed by the company's response to each issue.
- c. It is not necessary to submit all lab chromatography data. Submit only representative chromatograms, which support your analytical methods. The original submission contained an excessive number of chromatograms, which made it difficult to locate information for review.

- d. The recommended format for the CMC section is attached.
- e. Provide Central Filing Numbers (CFN) for each site used for manufacturing and controlling drug substance and drug product including contractors, packagers and/or testing labs, for example. All sites should be ready for inspection at time NDA is submitted to FDA.

With respect to other sections, Pharmacology/Toxicology and Pharmacokinetics, it is unclear from current submission what will be submitted in the future.

The agency will need to re-evaluate the data provided in a resubmission; with deficiencies to be determined in accordance with current practices and standards.

4. **The proposed product labeling is being submitted for discussion pertaining to the relevance, if any, of existing diclofenac labeling for oral products to the labeling for this topical diclofenac product (see Attachment #5).**

FDA Response: The existing labeling for diclofenac products is regarded as a basis for considering the appropriate labeling for new products that include this substance. Differences in labeling may reflect data showing that the new product differs significantly in its adverse event profile, e.g., data showing a lessened likelihood and/or severity of certain adverse events compared to current products, and/or data regarding new or different AE patterns associated with the new route of administration.

5. **Dimethaid is requesting that the PAI be scheduled as early as possible following the submission of the NDA resubmission document (see Attachment #3).**

FDA Response: FDA expects that all sites will be prepared and ready for site inspections when an NDA is submitted.

6. **Please confirm that a "Pediatric Waiver" for this product is appropriate.**

FDA Response: FDA finds this acceptable, for an indication of osteoarthritis (since OA is a rare condition in the pediatric population).

7. **In accordance with previous conversations with the Division staff, it is our understanding that the Nonclinical Pharmacology and Toxicology, Human**

Pharmacokinetic and Bioavailability and Microbiology sections have been reviewed in its entirety by the FDA and that any/all issues on the material submitted to date have already been raised. Please confirm this.

FDA Response: FDA does not confirm. FDA would need to fully review any new application in order to determine the deficiencies in that application.

ADDITIONAL COMMENTS:

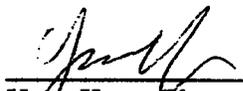
Sponsor inquired if they could cross-reference to the withdrawn NDA 20-947. FDA stated the need to review the application as if it was an entirely new application. Prior to withdrawal of NDA 20-947, the review had not been completed, so there may be additional deficiencies not yet identified at the time of withdrawal. Hence, the sponsor needs to submit the new NDA application in its entirety without cross-referencing to the withdrawn NDA 20-947.

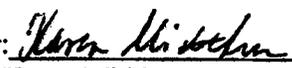
Pharmacology/Toxicology

FDA inquired if sponsor performed any pre-clinical tests with the proposed topical drug product. Sponsor indicated that only skin sensitivity studies were conducted.

ACTION ITEMS:

1. Sponsor will submit protocol (Study #RA-CP-109) formally to IND including proposed changes (e.g., statistical changes, primary endpoints, extension of 6-week study, etc.). Also, sponsor will submit focused questions on proposed protocol for FDA's review and feedback.
2. FDA will review previous application to identify any significant issues regarding Pharmacology/Toxicology or Biopharmaceutics and inform the sponsor.
3. FDA will inform sponsor whether the new NDA needs to be submitted in its entirety or whether the withdrawn NDA 20-947 can be cross-referenced.
4. FDA will convey minutes to sponsor within 30 days of meeting.
5. FDA will convey minutes of August 25, 1999, meeting to the sponsor.


7-19-00
Yoon Kong, Pharm.D.
Project Manager

Concur:  7-19-00
Karen Midthun
Division Director, DAAODP

IND 42,773
Pennsaid (difloclofenac topical lotion) Lotion
Pre-NDA Meeting
June 5, 2000
Page 8

Addendum: Post-sponsor meeting, FDA notes that the sponsor should submit all relevant information in their new NDA application.

Meeting minutes of August 25, 1999, were faxed to sponsor on June 6, 2000, and were subsequently mailed to sponsor on June 23, 2000.

Statistical Comments:

With respect to study (#RA-CP-109), the definition of ITT population is too exclusive. FDA suggests that the ITT population should include all patients who are randomized, have baseline measurements and have taken at least one dose of medication. Sponsor should propose a conservative method (in addition to the one specified in this protocol) to deal with missing values, to ensure that sensitivity of efficacy results can be adequately assessed.

IND 42,773
Pennsaid (difloclofenac topical lotion) Lotion
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Page 9

cc: IND # 42,773
HFD-550/Div File
HFD-550/J.Witter/K.Midthun
HFD-550/H.Amouzadeh/B.Osterberg
HFD-550/Sue-Ching Lin/M.Zarifa
HFD-725/L.Lu/Stan Lin
HFD-880/A.Adebowale/D.Bashaw
HFD-550/L.Vaccari
HFD-550/Y.Kong

Drafted by: Y.Kong/ 6-16/00
Initial by: R.Osterberg/7-5-00
L.Lu/7-6-00

Final by: K.Midthun/7-19-00

MEETING MINUTES



MEETING MINUTES

Meeting Date: August 25, 1999

Time: 1:30 - 4:00 p.m.

Location: CORP S-300

IND# 42,773

NDA# 20-947

Drug Name: Pennsaid (diclofenac) topical lotion

Sponsor: Dimethaid Research, Inc.

Type of meeting: Guidance

Attendees:

FDA

John E. Hyde, Ph.D., M.D.,
Deputy Division Director
Kent Johnson, M.D., Medical Officer
Constance Lewin, M.D., Project Manager
Stan Lin, Ph.D., Statistical Team Leader
James Witter, M.D., Medical Officer
Anthony Zeccola, Chief, Project Management Staff

Sponsor

Rebecca E. Keeler, President & CEO
George E. Markus
Director, Regulatory Affairs
Rheumatology Consultant
J. Zev Shainhouse, M.D.
Medical Director

b(4)

Meeting Chair: John E. Hyde, Ph.D., M.D.

Meeting Recorder: Constance Lewin, M.D.

Background Summary:

Sponsor requested this meeting to discuss items related to the clinical development program for this product. NDA 20-947 had previously been withdrawn; IND 42,773 is still active. Sponsors provided specific items for discussion in an August 6, 1999, meeting background package that was sent as desk copies only. However, upon the Division's recommendation, sponsor agreed that it would be more productive to focus discussion on the general development plan rather than the meeting-package questions.

Meeting Objective:

To provide guidance to sponsor on its clinical development plan

Discussion Points:

The Division opened the meeting by stating that this would be an informational meeting, not an End-of-Phase 2 meeting. As such, no agreements would be entered into.

Sponsor distributed a handout (Attachment 1) that contained all slides shown at the meeting. Sponsor then presented its slideshow, discussing each slide in the order presented in Attachment 1.

Participants discussed NSAID GI side effects. _____ sponsor's rheumatology consultant, spoke briefly about other applications he has been involved in. _____ also spoke about what he thought might be appropriate clinical trial designs for sponsor's product, stating that a knee study could be helpful but that the _____ that sponsor had done turned out to have difficulties that he had seen with other products. _____ went on to express his view that a topical NSAID could empower patients to take a stronger role in their own pain control.

b(4)

The Division told sponsor that it still wanted two studies to be done, explaining that although the regulations may allow for a single study in special circumstances, that is not the norm. The Division stated that there is concern regarding efficacy and that there should be replication of any single study where results appear successful. The Division informed sponsor that it hoped that the present meeting would afford participants an opportunity to discuss how that replication might be done.

The Division informed sponsor that the knee-study database does not clearly show robustness. Further, if such study were successful, sponsor would need to replicate these results, especially since the _____ failed. Sponsor responded that if they were to receive approval, the worst case would be that their product would not be as effective as others out on the market. The Division reminded sponsor that such a statement assumes that the product actually works and that sponsor still had to show efficacy. Secondly, implicit claims for safety would need to be substantiated. Sponsor stated that all relevant information in this regard had been submitted and reviewed. The Division informed sponsor that the information was not fully reviewed because the NDA was withdrawn prior to the completed review.

b(4)

Participants discussed powering of studies, safety and efficacy. The Division informed sponsor that there have been no adequately powered studies to show no difference between acetaminophen and NSAIDs. Sponsor stated that the therapeutic-to-toxic ratio of its product suggests that the relevant parties can be more liberal in reviewing the data, provided the data were looked at rigorously. The Division informed sponsor that it does not work that way: the Division does not want, for example, one out of every 20 products on the market to be inactive. Sponsor asked whether it would be possible to receive approval based on safety and then do another study once the product is approved. The Division responded no.

Participants discussed the product's active ingredient. The Division reminded sponsor that the active ingredient may have both positive and negative activity but said that no specific problematic issues are being raised at this time. Sponsor stated that the safety profile of its product is acceptable and that statistical significance at $p = 0.003$ was shown in its efficacy study. The Division concurred but stated that two studies would be needed, each with a p value of less than or equal to 0.05.

The Division informed sponsor that there is concern over the trial design, that the blind could be broken because patients using the drug product might be able to tell that they are and, consequently, influence study results. In addition, the Division stated that the data need to be reviewed before a determination of efficacy is made. Sponsor stated that the NDA review came to a halt because of PAI problems.

The Division told sponsor that for a _____ indication, there should be successful trials involving more than one site, per a recent OA guidance meeting. Sponsor was also informed that four studies in total, not two, may actually be needed. In response to Division inquiry, sponsor stated that it had not done any _____ with its product.

Participants further discussed potential trial designs, and the Division emphasized its earlier recommendation that sponsor do another study. Sponsor asked whether it could simultaneously refile to reactivate the NDA review, get a site audit, and discuss replication of the knee study. The Division informed sponsor that those are questions for an End-of-Phase 2 meeting but that sponsor has the option of filing the application, in which case the Division would make a determination regarding fileability. The Division told sponsor that it would prefer to discuss what went wrong with the _____ and asked sponsor whether it believed the Division should ignore the _____ evidence. Sponsor responded that, no, the Division should not ignore those results.

b(4)

The Division informed sponsor that it should establish that the product works consistently where applied because, in the Division's opinion, if the product were approved at this juncture, patients would _____ and there is no evidence that _____. The Division stated its strong preference to see the product work _____. The Division also stated its view that patients would be unlikely to use the product four times a day on the knee and that many patients were lost in the knee study. Sponsor responded that it did not believe the patient loss was due to the treatment regimen.

b(4)

The Division asked for sponsor's opinion on why the _____. Sponsor responded that it did not think there was a sufficient standardization of all patients and that patients may not have been evenly distributed.

b(4)

The Division asked sponsor what sort of labeling it envisioned (i.e., whether the product would be considered add-on or NSAID-sparing therapy). Sponsor's response was that it did not expect either the product to be used as either an add-on or NSAID-sparing agent but, rather, that the product would be used before NSAIDs. Sponsor said that the proposed label was submitted with the original submission.

Participants discussed the potential benefits of a topical NSAID and potential labeling _____ on knee studies. The Division told sponsor that if there are successful knee studies _____ the Division would want to know _____. Sponsor responded that it believes that the _____ a good model to study.

Participants discussed whether flares should be addressed in inclusion/exclusion criteria of future studies. The Division responded that many arthritis studies are flare studies.

b(4)

Participants returned to discussion of a _____. Sponsor asked the Division if another _____ would be required. The Division stated that it would be open to listening to sponsor if sponsor wanted to educate the Division on why it should not be expected. Participants then discussed how convincing evidence might be gathered. The Division stated that if a study were done where the product was applied to _____ a knee on the same subject and if _____ improved _____ that would be good evidence that the product works locally. The Division suggested that sponsor consider using AUSCAN and _____ as primary endpoints when designing a trial.

The Division expressed its belief that it would be to sponsor's advantage to come up with a successful _____. Sponsor asked, if it repeated the knee study and added some oral comparator, would that meet efficacy requirements? The Division responded that _____ are suggested for approvals. Sponsor then asked whether the label would include _____ if there were a successful trial involving _____ one knee. The Division responded that, so far, all OA approvals state that the products are approved for _____ however, sponsor could make its argument for something else if it presented a successful _____ trial.

b(4)

Participants discussed sponsor's desire to resubmit the NDA. The Division informed sponsor that it could resubmit the NDA at this time but that, without an additional study, the Division would probably find the submission inadequate for filing purposes. The Division told sponsor that, if the NDA were resubmitted and the Division did indeed decide there were fileability concerns, sponsor could avail itself of the Agency's appeal process. Sponsor asked about the possibility of receiving accelerated approval, to which the Division responded that such procedure would not be applicable in this case.

Sponsor stated that it would consider doing another _____. Sponsor asked, if another _____ showed results equal to oral NSAIDs, would that be acceptable? The Division responded no, that sponsor would have to beat a control and that any oral-agent studies would have to be double-dummy studies.

b(4)

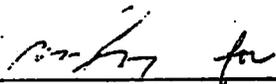
Sponsor asked for the Division's rationale behind its view that the application as it stands would likely be insufficient for filing purposes. The Division informed sponsor that for an application to be fileable, it should be complete. Given that sponsor has one successful trial at this point, and the Division has stressed the need for replication, there would likely be fileability issues if a second study were not submitted.

The Division recommended that sponsor strongly consider labeling when making clinical development plans for this product. The Division pointed out that, if sponsor were seeking to gain approval for the product to be used as a standard therapy on a daily basis, there would probably be more rigorous expectations than if sponsor wanted the product to be approved as an add-on therapy or for use on an as-needed basis. The Division closed the meeting with a recommendation that, for more specifics, sponsor come back at the appropriate time for an End-of-Phase 2 meeting.

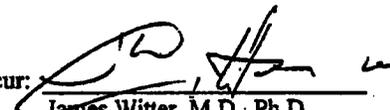
Action Items/Agreements reached: None

Attachment:

Copy of sponsor's presentation slides



Constance Lewin, M.D.
Project Manager

Concur: 

James Witter, M.D., Ph.D.

IND 42,773
NDA 20-947
Page 5

cc:

IND 42,773
NDA 20-947
HFD-550/Division file
HFD-550/K. Midthun
HFD-550/K. Johnson
HFD-550/Sue-Ching Lin/M. Zarifa
HFD-550/H. Amouzadeh/B. Osterberg
HFD-550/Y. Kong
HFD-725/Stan Lin
HFD-550/J. Witter
HFD-550/L. Vaccari

Drafted by: Constance Lewin

Initialed by: James Witter 
Final by:

22-OCT-1998

DF

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

OCT 21 1998

Application: NDA 20947/000
Stamp: 16-DEC-1997 Regulatory Due: 08-JAN-1999
Applicant: DIMETHAID
144 STEELCASE RD WEST, L3R 3J9
MARKHAM, ONTARIO, CA

Priority: 3S
Action Goal:
Brand Name: PENNSAID(DICLOFENAC
SODIUM)1.5% TOP LOTI
Org Code: 550
District Goal: 08-SEP-1998

Established Name:
Generic Name: DICLOFENAC SODIUM
Dosage Form: LOT (LOTION)
Strength: 1.5%

FDA Contacts: V. LUTWAK (HFD-550) 301-827-2090 , Project Manager
C. YACIW (HFD-830) 301-827-2296 , Review Chemist
H. PATEL (HFD-550) 301-827-2507 , Team Leader

Overall Recommendation:

WITHHOLD on 21-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____ DMF No:
_____ AADA No:

b(4)

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 20-OCT-1998
Decision: WITHHOLD
Reason: FIRM NOT READY
Responsibilities: FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE
TESTER

Establishment: _____ DMF No: _____
_____ AADA No:

b(4)

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-OCT-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment: _____ DMF No:
_____ AADA No:

b(4)

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-JAN-1998
Responsibilities: DRUG SUBSTANCE RELEASE
TESTER
FINISHED DOSAGE RELEASE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

TESTER
FINISHED DOSAGE STABILITY
TESTER

Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: _____

DMF No:
AADA No:

b(4)

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 13-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE RELEASE
TESTER
FINISHED DOSAGE STABILITY
TESTER

CC NDA 20947
DIV. FILE HFD-550

Minutes

Type of Meeting: Teleconference

NDA 20-947 Pennsaid

Sponsor: Dimethaid Research

Date: July 23, 1998

Attendees:

FDA: M Averbuch, C Yaciw, V Lutwak

Dimethaid: D Cymerman, K. Williams, C Achkouti, Z Shainhouse, P Varaday

The telecon addressed questions in a fax communication (see attached) requesting comments on some proposed changes in specifications.

1-3 are acceptable.

4- Keep assay for all labeled ingredients. This is required by law.

5- Approval to remove this test.

6- For all new testing facilities inspections are required by the FDA for compliance to meet GLP. The sponsor will send all information on the new test laboratory and will notify us when laboratories are no longer on contract.

cc:
NDA
DivFile
HFD-550/ M Averbuch/ C Yaciw/ V Lutwak

Proposed changes to Pennsaid Specifications

We are contemplating to make some modifications to the Pennsaid Specifications that in our opinion will more accurately reflect standard industrial practices. The following is a brief outline of what we would like to do:

- 1 • To reduce in-process bulk testing to physical parameters only i.e. do Specific Gravity and pH tests.
- 2 • To update our Finished Product Active Specification Release limits to between 90% - 110%.
- 3 • To amend the Impurity Specification Stability Limits to reflect ICH guidelines i.e. unknown impurity < 0.1%, Known impurity < 0.2% and Total impurity < 2%.
- 4 • _____

5 • The Viscosity results were negligible (approximately _____) and therefore we would like this test to be removed from all the specifications.

6 In addition to the above we have changed: our contract manufacturing site, the supplier for one of the excipients (Glycerin) and we are using an additional testing facility.

While we appreciate that it is unusual to revise product specifications at this stage in the submission process, your indulgence would be sincerely appreciated in this instance.

Looking forward to receiving your comments and would like to set a convenient date and time to discuss the above in more details.

b(4)

Minutes

Type of Meeting: Teleconference

*but to doc.
7/28/97*

NDA 20-947 Pennsaid

Sponsor: Dimethaid Research

Date: ~~February~~ ^{July} 23, 1998

Attendees:

FDA: M Averbuch, C Yaciw, V Lutwak

Dimethaid: D Cymerman, K. Williams, C Achkouti, Z Shainhouse, P Varaday

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cc:

NDA

DivFile

HFD-550/ M Averbuch/ C Yaciw/ V Lutwak

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b(4)

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Looking forward to receiving your comments and would like to set a convenient date and time to discuss the above in more details.

Minutes

Type of Meeting: Teleconference

NDA 20-947, Pennsaid

Sponsor: Dimethaid Research

Date: February 23, 1998

Attendees:

FDA: L Lu, V Lutwak

Dimethaid: C. Wong , K. Williams, Dilys Williams, W Johnson, P Varaday

This short telecon was requested by us to address questions regarding the electronic submission of the NDA for the statistician.

1. The statistician would like the entire NDA on diskette.
2. Requirements for the data sets with full descriptions of all data endpoints..
3. Annotated case report forms
4. Clarification on dropouts- last observation carried forward.

cc:

NDA 20-947

Div. File

HFD-550/CSO/ V Lutwak

Meeting Minutes

Type of Meeting: Team Meeting

Subject: Pennsaid

NDA: 20-947

Sponsor: Dimethaid

Date: June 22, 1998

Attendees: M Averbuch, C Yaciw, B Taneja, V Lutwak

Overview/Background: See previous minutes. The reviewers have completed their drafts/reviews.

- ▶ After first consulting with John Hyde, we may have a teleconference with the sponsor outlining their options.

Provide the sponsor with list of what they need upon resubmission of the NDA: labeling (hard and electronic), one more study, chemistry and manufacturing deficiencies addressed.

Action Item: Draft letter and circulate.

cc:

NDA

DivFile

HFD-880/ D Wang

HFD-550/ M Averbuch/ B Taneja/ C Yaciw/ W Coulter/ V Lutwak

Div 1152

Meeting Minutes

Type of Meeting: Team Meeting

Subject: Pennsaid

NDA: 20-947

Sponsor: Dimethaid

Date: May 21, 1998

Attendees: M Averbuch, C Yaciw, B Taneja, V Lutwak

PK:

D. Wang was not present but stated before the meeting that there are no outstanding PK issues, at this time. She will have her review by the end of May.

Pharm/Tox:

W. Coulter was not present but stated that his first draft is ready..

Chemistry:

C. Yaciw stated that the review is in progress and that the lists of deficiencies is not complete.

It was noted that the sponsor failed to submit microbiology section which was discussed at the pre NDA meeting.

The inspection is scheduled for the new manufacturer.

Clinical: M. Averbuch

Statistical: B. Taneja

The two studies are reviewed. Stat will co-review with clinical in a combined review.

Deadline for the first draft is the end of May. Safety studies are under review.

Progress to date:

Reviews are progressing on schedule. All the first draft will be ready by the end of May.

Action Item:

Call sponsor and ask for the microbiology in a single volume for consultation.

cc:

NDA

DivFile

HFD-880/ D Wang

HFD-550/ M Averbuch/ B Taneja/ C Yaciw/ W Coulter/ V Lutwak

Minutes

Type of Meeting: Team Meeting
NDA 20-947, Pennsaid

Sponsor: Dimethaid Research

Date: May 1, 1998

Attendees: M. Averbuch, C Yaciw, D Wang, D Bashaw, B Taneja, V Lutwak

The meeting was in response to the notification that the manufacturer of the drug product would have to change due to reasons beyond the sponsor's control. It is unusual for this to happen during the review of a NDA. The company is putting forth a good faith effort to get the problem resolved.

Chemistry:

The new manufacturer has to supply the following information:

The CMC data for the change is as follows:

1. The name and street address for the new manufacturing facility should be submitted ASAP so that we will have time to schedule the inspection. The inspection will be much easier if the facility already makes product for the US market.
2. A list of all changes in manufacturing process including process controls.
3. Batch records for the new manufacturing facility.
4. Comparative data for the old vs the new sites, i.e., data showing that the product from the new facility is the same as that from the old site. This requires that at least one batch (at least 1/10th the proposed commercial batch size) be made at the new site.
5. Dimethaid needs to take into consideration that we have a strict legal deadline for action on this NDA and that major changes such as this are not done quickly.

Other: Pennsaid is a single phase liquid and not a lotion.

Status of Reviews: The reviewers will continue their reviews.

D1
120-947

Meeting Minutes

Type of Meeting: Team Meeting

NDA: 20-947

Sponsor: Dimethaid

Date: April 21, 1998

Attendees: M Averbuch, D Bashaw, C Yaciw, B Taneja, V Lutwak,

This brief meeting was held to update the reviewers on the following:

New Statistician: Baldeo Taneja will replace Laura Lu.

The Nomenclature Committee found no objections to the tradename, Pennsaid. DSI needs a memo from MO(per Tony El Hage).

Reports from reviewers:

Stat will complete first draft by the end of May.

Chem is 3/4 complete, but noted that there are deficiencies that need attention.

Clinical is halfway through the review. There are two studies: one is acceptable and the other is still under review. At the present, there are no safety issues.

Biopharm: Dennis said the D Wang will have the draft by the end of May. It is a small PK section

Preclinical: W Coulter, who could not attend, said that his first draft will be ready by the end of May.

Action Items:

V will call Tony Carreras on May 1 when he returns to determine what type of memo is needed.

Check the archival copy for a chemistry jackets.

Check on the ERR.

Provide to the sponsor the list of deficiencies from the chemistry reviewer.

cc:

NDA

Div. Files

HFD-880/ D Wang/ D Bashaw

HFD-550/ M Averbuch/ B Taneja/ C Yaciw/ V Lutwak



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

530
Luttwak

Food and Drug Administration
Rockville MD 2085

NDA 20-947

FEB - 6 1998

Dimethaid Research Inc.
Attention: J. Zev Shainhouse, MD, BSc, FRCPC
Medical Director
1405 Denison Street
Markham, ON
L3R 5V2
Canada

Dear Dr. Shainhouse:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pennsaid (diclofenac sodium lotion) 1.5%

Therapeutic Classification: Standard

Date of Application: December 15, 1997

Date of Receipt: January 8, 1998

Our Reference Number: NDA 20-947

Please note that under section 736(e) of the Prescription Drug User Fee Act 1992 (PDUFA), an application is considered incomplete and is not accepted by the Agency until all fees owed have been paid.

This is to notify you that the Agency has received all fees owed, and your application has been accepted for review for filability as of January 8, 1998.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act in accordance with 21 CFR 314.101(a).

NDA 20-947

Page 2

Should you have any questions, please call: Vickey Lutwak, Project Manager, (301) 827-2522.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

CEK 2/6/98

Chin Koerner, M.S.
Chief, Project Manager
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

NDA 20-947
Page 3

cc:

NDA 20-947
Div File
HFD-550/ CSO/ V Lutwak
HFD-550/ J Hyde/ M Averbuch/ W Coulter/ C Yaciw
HFD-725/ M Huque/ L Lu
HFD-880/ D Bashaw/ D Wang