

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-947

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW



NDA 20-947

**Pennsaid®
(Diclofenac Sodium) Topical Solution**

Dimethaid International Inc.

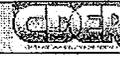
Olen M. Stephens

**Division of Pre-Marketing Assessment I, Branch II, ONDQA
for the
Division of Anesthesia, Analgesia and Rheumatology
Products,
HFD-170**



Table of Contents

| | |
|---|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 8 |
| I. Recommendations..... | 8 |
| A. Recommendation and Conclusion on Approvability | 8 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8 |
| II. Summary of Chemistry Assessments..... | 8 |
| A. Description of the Drug Product(s) and Drug Substance(s)..... | 8 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 11 |
| A. Reviewer's Signature..... | 11 |
| B. Endorsement Block..... | 11 |
| C. CC Block | 11 |
| Chemistry Assessment..... | 12 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data..... | 13 |
| S DRUG SUBSTANCE [Name, Manufacturer]..... | NA |
| P DRUG PRODUCT [Name, Dosage form]..... | 23 |
| A APPENDICES | 39 |
| R REGIONAL INFORMATION | 39 |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 | 42 |
| A. Labeling & Package Insert | 42 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | 42 |
| III. List Of Deficiencies To Be Communicated..... | 42 |



Chemistry Review Data Sheet

1. NDA 20-947
2. REVIEW #: 4
3. REVIEW DATE: 22-JUN-2009
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Chemistry Review #1 Cycle

Original submission
Chemistry Review #1
Withdrawal of NDA by applicant

Document Date

15-Dec-1997
02-May-1998
26-Oct-1998

Chemistry Review #2 Cycle

Resubmission (AZ)
Amendment (BC)
Amendment (BC)
FDA issued a "not approvable" letter

Document Date

07-Aug-2001
13-Feb-2002
07-May-2002
07-Aug-2002

Chemistry Review #3 Cycle

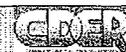
Resubmission (AZ)
Amendment (BZ) (mock-up container and carton labels)
Amendment (BC) (updated stability data)
Amendment (BC) (container closure changes)
Amendment (BZ) (response to labeling comments)
Amendment (BC) (drug product specification, etc)
Amendment (BZ) (replacing the 10/26/06 amendment,
based on the 10/26/06 telecon discussion)

Document Date

28-Jun-2006
17-Aug-2006
17-Aug-2006
12-Oct-2006
25-Oct-2006
26-Oct-2009
27-Oct-2006



CHEMISTRY REVIEW



Chemistry Review Data Sheet

| | |
|---|-------------|
| Amendment (AZ) (response to comments on the volume of 40 drops) | 08-Nov-2006 |
| Amendment (BC) (USP <671> results) | 10-Nov-2006 |
| Amendment (BC) (revised drug product specification) | 15-Nov-2006 |
| Chemistry Review #3 | 21-Nov-2006 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Resubmission (AZ) | 04-Feb-2009 |
| Amendment (BC) (response to information request) | 27-APR-2009 |
| Amendment (BC) (response to information request) | 11-JUN-2009 |

7. NAME & ADDRESS OF APPLICANT:

Name: Nuvo Research Inc.
7560 Airport Road
Unit 10
Address: Mississauga, ON
Canada L4T 4H4
Representative: Mimi Diva Brennan
Director, Clinical Research and Regulatory Affairs
Telephone: 905-673-6980 (telephone)
905-673-1842 (fax)

US Agent:

Name: Dr. Brad Galer
Address: 2-1740 Lenape Road
West Chester, PA 19382
Telephone: 610-675-5884 (telephone)

8. DRUG PRODUCT NAME/CODE/TYPE:

- Proprietary Name: Pennsaid® Topical Solution
- Non-Proprietary Name (USAN): diclofenac sodium topical solution
- Code Name/# (ONDC only):
- Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S



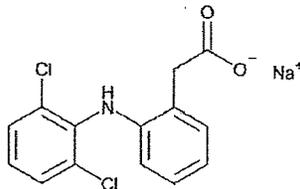
CHEMISTRY REVIEW



Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), resubmission
10. PHARMACOL. CATEGORY: NSAID
11. DOSAGE FORM: solution
12. STRENGTH/POTENCY: 1.5% w/w (16 mg/mL)
13. ROUTE OF ADMINISTRATION: topical
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt



$C_{14}H_{10}Cl_2NNaO_2$ MW 318.13

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|---------------------------|
| | | | | 1 | Adequate | 22-JUN-2009 | Reviewed by this reviewer |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 4 | | | |
| | | | | 1 | Adequate | 22-JUN-2009 | Reviewed by this reviewer |

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Note: Refer to page 22 of CMC review #2 for the review of the container closure system. Also see page 22 of CMC review #3 and page 20 of this review for information regarding the HDPE containers introduced in this review cycle.

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-----------------------------|
| IND | 42,773 | (diclofenac sodium topical) |

b(4)

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|----------------|------|----------|
| Biometrics | N/A | | |



CHEMISTRY REVIEW



Chemistry Review Data Sheet

| | | | |
|--------------------|--|--------|-------------|
| EES | Pending | | |
| Pharm/Tox | N/A | | |
| Biopharm | N/A | | |
| LNC | N/A | | |
| Methods Validation | N/A, according to current ONDQA policy | | |
| OPDRA | | | |
| EA | Categorical exclusion (see review #2) | | |
| Microbiology | Adequate | 2/7/02 | Bryan Riley |



The Chemistry Review for NDA 20-947

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC) perspective, this NDA is approvable pending:

1. Office of Compliance overall cGMP recommendation of the commercial manufacturing and testing facilities listed in the NDA.
2. Sufficient response(s) to pending CMC deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following are CMC agreements (i.e., these are NOT post-marketing commitments or requirements and will NOT be posted on FDA's website as per FDAAA):

b(4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The active ingredient is diclofenac sodium, USP, manufactured by _____ Detailed CMC information on the drug substance is referenced to DMF _____ which was recently reviewed by this reviewer on 22-JUN-2009 and found to be adequate. The drug substance meets current USP specifications and is tested per USP monograph for diclofenac sodium.

b(4)

(2) Drug Product

Pennsaid® Topical Solution contains 1.5% w/w diclofenac sodium as the active ingredient. The drug product also contains 45.5% w/w of dimethyl sulfoxide (DMSO), which was listed as one of the inactive ingredients by the applicant. However, DMSO is known to possess anti-inflammatory activity and is the active ingredient of Rimso®-50,



CHEMISTRY REVIEW



Executive Summary Section

an aqueous solution containing 50% w/w of DMSO, which was approved on 4/4/1978 in NDA 17-788.

The packaging system for the finished topical solution includes a white high-density polyethylene (HDPE) bottle with a low-density polyethylene (LDPE) dropper cap and is available in three fill sizes: 15 mL (physician sample size), 60 mL, and 150 mL. —

b(4)

B. Description of How the Drug Product is Intended to be Used

Pennsaid® is intended to be applied topically to the knees four times a day for relief of signs and symptoms of osteoarthritis. The dose is 40 drops (approximately 1.2 mL) per knee.

The expiration dating is supported by stability data from _____ of each fill size, which includes up to 12 months data under 25°C/60% RH storage, 12 months data under 30°C/60% RH storage, and 6 months data under 40°C/75% RH storage. Stability data under accelerated conditions _____ the specifications for Impurity A _____. Therefore, the expiry date is limited based on ICH Q1E guidelines and up to 36 month long term supportive stability data. Pennsaid® Topical solution in 15- and 60-mL HDPE bottles with an LDPE closure is stable for 18 months when stored upright [see USP Controlled Room Temperature]; the shelf life for Pennsaid® Topical solution in 150-mL HDPE bottles with an LDPE closure is 15 months.

b(4)

The recommend storage condition is 25°C (77°F); excursions permitted to 15-30°C (59- 86°F).

C. Basis for Approvability or Not-Approval Recommendation

This NDA was first submitted on 12/15/97 and is now in its fourth review cycle. In the most recent review cycle, CMC deficiencies were identified concerning the _____ the toxicological consequences of 45.5% DMSO concentrations in the drug product _____. Updated stability data was included in the current submission.

b(4)

Stability data under accelerated conditions exceeded the specification for _____ the Impurity A specification in the 60-mL bottle at 3 months. Therefore, the supportive stability data is limited in its use to establish an expiry date (ICH Q1E). Primary stability data also demonstrated a _____ more prevalent under intermediate and accelerated

b(4)



CHEMISTRY REVIEW



Executive Summary Section

conditions. The applicant will address _____ by shipping the bottles in an upright orientation and labeling boxes with directions to maintain this orientation.

b(4)

The expiration dating period grantable for the Pennsaid® Topical solution in 15- and 60-mL HDPE bottles with an LDPE closure is 18 months when stored upright under conditions of 25°C (77°F); excursions permitted to 15- 30°C (59-86°F) [see USP Controlled Room Temperature]; the expiration dating period for Pennsaid® Topical solution in 150-mL HDPE bottles with an LDPE closure is 15 months. This should be included in the action letter.

The applicant has addressed the toxicological consequences of 45.5% DMSO and specification limit for the potential _____ with non-clinical data (see the non-clinical review). However, using 45.5% DMSO in the drug product, increases the potential to generate a large _____. In previous review cycles, the drug product used _____ that demonstrated a high susceptibility to _____. By recommendation from the Division, the applicant _____

b(4)

The applicant has submitted _____ in the current review along with new primary stability data using the HDPE bottles. The data identified _____ which have been qualified through literature research. Data from _____ demonstrates that _____ appreciably in the drug product through 12-months. While the in-use stability study and _____ that accumulate inside the Pennsaid® bottles, concerns remain regarding _____. The applicant was instructed (19-JUN-2009) to evaluate the potential _____

b(4)

A re-evaluation was submitted for all the facilities for the manufacturing, testing, and packaging of the drug substance and drug product to the Office of Compliance and is pending review.

Therefore, NDA 20-947 is approvable from a CMC perspective pending satisfactory evaluation for manufacturing, testing and packaging facilities and the evaluation of _____ product through anticipated normal use.

b(4)



III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

C. CC Block

31 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Olen Stephens

6/22/2009 12:43:55 PM

CHEMIST

Approvable pending results of in-use leachable study regarding product
label

Ali Al-Hakim

6/22/2009 12:58:54 PM

CHEMIST

NDA 20-947

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

Dimethaid International Inc.

Sue-Ching Lin

Review Chemist

**Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch V
for
Division of Anesthesia, Analgesia, and
Rheumatology Products (DAARP)**



Table of Contents

CMC Review Data Sheet3

The Executive Summary7

 I. RECOMMENDATIONS7

 A. Recommendation and Conclusion on Approvability7

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable7

 II. SUMMARY OF CHEMISTRY ASSESSMENTS7

 A. Description of the Drug Product and Drug Substance7

 B. Description of How the Drug Product is Intended to be Used8

 C. Basis for Approvability or Not-Approval Recommendation8

 III. ADMINISTRATIVE9

CMC Assessment.....10

 I. UPDATED STABILITY DATA11

 II. REVISED DRUG PRODUCT SPECIFICATION13

 III. UPDATED LABELING16

 IV. VOLUME OF EACH APPLICATION OF 40 DROPS21

 V. UPDATED DRUG SUBSTANCE DMF21

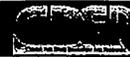
 VI. EXECUTED BATCH RECORDS22

 VII. ADDITIONAL CONTAINER CLOSURE SYSTEM22

 VIII. ESTABLISHMENT INSPECTION27

 IX. LIST OF DEFICIENCIES COMMUNICATED AND RESOLVED29

 X. LIST OF PENIDNG DEFICEINCIES32



CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 20-947
2. REVIEW #: 3
3. REVIEW DATE: 21-Nov-2006
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

| Chemistry Review #1 Cycle | Document Date |
|----------------------------------|----------------------|
| Original submission | 15-Dec-1997 |
| Chemistry Review #1 | 02-May-1998 |
| Withdrawal of NDA by sponsor | 26-Oct-1998 |

| Chemistry Review #2 Cycle | Document Date |
|--------------------------------------|----------------------|
| Resubmission (AZ) | 07-Aug-2001 |
| Amendment (BC) | 13-Feb-2002 |
| Amendment (BC) | 07-May-2002 |
| FDA issued a "not approvable" letter | 07-Aug-2002 |

6. SUBMISSION(S) BEING REVIEWED:

| Subject of this review | Document Date |
|---|----------------------|
| Resubmission (AZ) | 28-June-2006 |
| Amendment (BZ) (mock-up container and carton labels) | 17-Aug-2006 |
| Amendment (BC) (updated stability data) | 17-Aug-2006 |
| Amendment (BC) (container closure changes) | 12-Oct-2006 |
| Amendment (BZ) (response to labeling comments) | 25-Oct-2006 |
| Amendment (BC) (drug product specification, etc) | 26-Oct-2006 |
| Amendment (BZ) (replacing the 10/26/06 amendment, based on the 10/26/06 telecon discussion) | 27-Oct-2006 |
| Amendment (BZ) (response to comments on the volume of 40 drops) | 08-Nov-2006 |
| Amendment (BC) (USP <671> results) | 10-Nov-2006 |
| Amendment (BC) (revised drug product specification) | 15-Nov-2006 |

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Dimethaid International Inc.
Address: Los Abedules, Appleby Gardens
St. James, Barbados
Representative: Dr. Frederick N. Ballantyne
2220 Chalkwell Drive
Midlothian, VA 23113-3884
U.S.A.
Telephone: 866-652-9473 (telephone)
866-652-9476 (fax)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pennsaid® Topical Solution
b) Non-Proprietary Name (USAN): diclofenac sodium topical solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), resubmission

10. PHARMACOL. CATEGORY: NSAID

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 1.5% w/w (16 mg/mL)

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

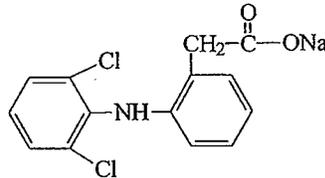
SPOTS product – Form Completed

Not a SPOTS product

CMC Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt



C₁₄H₁₀Cl₂NNaO₂ MW 318.13

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|---------------------------|
| | | | | 1 | Adequate | 11/20/06 | Reviewed by this reviewer |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Note: Refer to page 22 of CMC review #2 for the review of the container closure system. Also see page 22 of this review for information regarding the HDPE containers proposed during this review cycle.

CMC Review Data Sheet

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-----------------------------------|
| IND | 42,773 | _____ (diclofenac sodium topical) |

b(4)

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|--|----------|-------------------|
| Biometrics | N/A | | |
| EES | Acceptable | 8/29/06 | S. Adams, HFD-322 |
| Pharm/Tox | N/A | | |
| Biopharm | N/A | | |
| LNC | N/A | | |
| Methods Validation | N/A, according to the current ONDQA policy | | |
| Division of Medical Errors and Technical Support (DMETS)* | The proprietary name Pennsaid is acceptable. | 11/30/06 | Jinhee Jahng |
| EA | categorical exclusion (see review #2) | | |
| Microbiology | Adequate | 2/7/02 | Bryan Riley |

*In addition to the comments on the proprietary name, DMETS also made comments on the container and carton labels in the 11/30/06 DMETS review. However, it appears that the comments in the 11/30/06 DMETS review regarding container and carton labels were based on the labels that were submitted in the 8/17/06 amendment. Note that the applicant has submitted the 10/25/06 amendment with revised labels in color version, in response to the CMC IR letter dated 10/20/06. All of DMETS comments have already been addressed in the 10/25/06 amendment. This reviewer sent an e-mail (through Dr. Ravi Harapanhalli) to Paul Balcer (project manager) and clinical reviewers on 11/30/06, informing the team that the issues have been addressed. During the 12/11/06 labeling meeting, the review team recommended to remove the graphic design of a tear drop from container and carton labels. Because the teardrop looks like an eye drop rather than a topical product. The review team is concerned that having this teardrop on the labels might encourage users to think that it may be used via the ophthalmic route. This comment was conveyed to the applicant by the project manager via the 12/14/06 information request letter.

Executive Summary Section

The CMC Review for NDA 20-947

The Executive Summary

I. RECOMMENDATIONS

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC) perspective, this NDA is approvable pending resolution of the deficiencies listed at the end of the review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

The active ingredient is diclofenac sodium, USP. It is manufactured by _____ Detailed CMC information on the drug substance is referenced to DMF _____ which was recently reviewed by this reviewer on 11/20/06 and found to be adequate. The drug substance meets current USP specifications and is tested per USP monograph for diclofenac sodium.

b(4)

(2) Drug Product

Pennsaid[®] Topical Solution contains 1.5% w/w diclofenac sodium as the active ingredient. The drug product also contains 45.5% w/w of dimethyl sulfoxide (DMSO), which was listed as one of the inactive ingredients by the applicant. However, DMSO is known to possess anti-inflammatory activity and is the active ingredient of Rimso[®]-50, an aqueous solution containing 50% w/w of DMSO, which was approved on 4/4/1978 in NDA 17-788.

The packaging system for the finished topical solution includes a white _____ bottle with a dropper cap and is available in three fill sizes: 15 mL (physician sample size), _____ and 60 mL, as proposed in the previous review cycle. In addition, a new _____ was proposed in this review cycle.

b(4)

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Pennsaid[®] is intended to be applied topically to the knees four times a day for relief of signs and symptoms of osteoarthritis. The dose is 40 drops (approximately 1.2 mL) per knee.

The applicant proposed an 18-month expiration period for the 15-mL fill size and a _____ expiration period for the _____ 60-mL, and _____ fill sizes. The expiration periods are supported by stability data from six to eight batches respectively of each fill size, which include 36 months data under 25°C/60%RH, 18 months data under 30°C/60%RH, and 6 months data under 40°C/75%RH.

b(4)

The recommend storage condition is 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

This NDA was first submitted on 12/15/97 and was later withdrawn by the sponsor on 10/26/98. Chemistry review #1 was completed on 5/2/98 and major deficiencies were conveyed to the applicant in an "information request" letter. The 8/7/01 resubmission made major changes to the manufacturing and control of the drug product. In reviewing the resubmission, deficiencies were found by this reviewer and were relayed to the applicant. These deficiencies involved drug product specification, stability data, post-approval stability protocol, labeling and others. The applicant adequately responded to the deficiencies in the 5/7/02 amendment.

As stated in the executive summary of chemistry review #2 of this NDA, there were no outstanding CMC issues from the last review cycle and thus this NDA was recommended for approval from CMC perspective, based on the information provided in the 8/7/01 resubmission and its subsequent amendments. However, the following information was updated in this review cycle: stability data, drug product specification, labeling, drug substance DMF, manufacturing batch records, and container closure system. Five CMC information request letters, dated 8/3/06, 8/10/06, 9/25/06, 10/20/06, and 11/2/06, were sent to the applicant during this review cycle. A telephone conference with the applicant was held on 10/26/06. The updated data and the applicant's response to the CMC comments have been reviewed and found to be deficient. A re-evaluation of all the facilities for the manufacturing, testing, and packaging of the drug substance and drug product was submitted to the Office of Compliance. All the facilities were found to be acceptable and an overall recommendation was issued by the Office of Compliance on 8/29/06.

Executive Summary Section

III. ADMINISTRATIVE

A. Reviewer's Signature: electronically signed in DFS

Sue-Ching Lin, M.S., R.Ph.

B. Endorsement Block: electronically signed in DFS

Ravi Harapanhalli, Ph.D.

C. CC Block: entered electronically in DFS

24 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Sue Ching Lin
12/15/2006 04:37:06 PM
CHEMIST

Ravi Harapanhalli
12/15/2006 04:50:30 PM
CHEMIST

CMC Branch Chief Memo

Ravi S. Harapanhalli, Ph.D.

Application: NDA 20-947

Date: December 15, 2006

CMC Primary reviewer: Sue-Ching Lin, R. Ph.

Recommendation: Approvable pending satisfactory resolution of listed deficiencies.

Notes:

Please see the detailed CMC review in DFS, written by Sue-Ching Lin. The NDA is fraught with major safety-related concerns due to the presence of significant quantities of a structural alert degradation product and large quantities of ——— extractables that result from the interaction of the formulation with the container closure system.

b(4)

Structural alert degradation product:

b(4)

b(4)

b(4)

b(4)

Although it is true that diclofenac itself _____ and is structural alert, the fact that diclofenac is a drug from which certain benefit is expected and that it has undergone adequate safety assessment previously would suffice to say, it's risk benefit is determined whereas that of the above degradation impurity is unknown. There is no benefit to derive from the degradation product, only the risk of it being genotoxic due to its structural alert moiety. Therefore, in consultation with the Pharm/Tox discipline, the following deficiency is recommended to be included in the action letter. The e-mail correspondence with the Pharm/Tox team leader is attached at the end.

Safety concerns with the extractables:

The firm proposed a change in the _____ since

b(4)

In support of this change, the firm provided a reference to the compliance with the food contact CFRs as follows:

b(4)

However, during this review cycle we asked the firm to provide additional data from the extractability studies using USP<661> and also to carry out USP<671> in support of the proposed changes. The data provided by the firm indicates that _____

b(4)

| TEST DESCRIPTION | LIMITS | RESULTS | STATUS |
|------------------|--------|---------|--------|
| | | | Pass |

b(4)

Thus, it can be seen from the above table that the drug product vehicle extracted _____ compared to the amounts extracted in the other three solvents. This is not unexpected since dimethyl sulfoxide is a strong extractant and is present in _____ in the formulation. It should be noted that the above extraction studies do not adequately represent the extent of interaction _____ with the formulation throughout the shelf life, which is proposed at _____. Potentially, significantly _____ of the product. Therefore, in consultation with the Pharm/Tox reviewer, the following deficiency was generated for inclusion in the action letter.

b(4)

E-mail correspondence with Pharm/Tox Supervisor:

From: Mellon, Dan

Sent: Friday, December 15, 2006 1:34 PM

To: Harapanhalli, Ravi S

Cc: Leshin, Lawrence; Lin, Sue Ching

Subject: RE: NDA 20-947: CMC Deficiencies

That makes sense to me! We can certainly cross that bridge when/if we come to it. I do think that the sponsor has pretty big challenge ahead of them, but time will tell!

Thanks again!

Dan

PharmTox Supervisor

DAARP

301-796-1256

From: Harapanhalli, Ravi S

Sent: Friday, December 15, 2006 1:31 PM

To: Mellon, Dan

Cc: Leshin, Lawrence; Lin, Sue Ching

Subject: RE: NDA 20-947: CMC Deficiencies

Good point Dan. I was thinking of modifying the comment to read "pending satisfactory safety assessment of the _____." caveat in the comment. If they qualify those extracts adequately, perhaps we cannot object to the use of _____. If they don't, then certainly the alternative is to use glass with minimal contact with _____

b(4)

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Mellon, Dan
Sent: Friday, December 15, 2006 1:01 PM
To: Harapanhalli, Ravi S; Lin, Sue Ching
Cc: Leshin, Lawrence
Subject: RE: NDA 20-947: CMC Deficiencies

Ravi and Sue Ching,

These look fine to both Steve and myself. I will include my concurrence with these recommendations in my memo as well, since there are toxicological implications.

Do you feel that the HDPE bottle will be feasible for such a product given the extractable info, assuming one gets approved? I would have thought that a glass bottle would be better, but you still have stopper/dispenser problems with extractable issues, so perhaps that is the best. Just curious.

Thanks to all of you!

Dan
PharmTox Supervisor
DAARP
301-796-1256

From: Harapanhalli, Ravi S
Sent: Thursday, December 14, 2006 7:38 PM
To: Rappaport, Bob A; Roca, Rigoberto A; Mellon, Dan
Cc: Harapanhalli, Ravi S; Lin, Sue Ching; Balcer, Paul
Subject: NDA 20-947: CMC Deficiencies

Attached are the three CMC deficiencies that will be included in the review and we are recommending "Approvable" from CMC perspective.

Dan: Please check the first deficiency as it pertains to genotoxic structural alert that we discussed this afternoon.

Thanks

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology,
and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

Overall recommendation:

In view of the potential safety issues surrounding the formation of a structural alert degradation product and high extraction of _____ of the container closure system by the formulation, we do not recommend the approval of this NDA. It is approvable pending satisfactory resolution of the three deficiencies listed at the end of this memo and included in the CMC review by Sue-Ching Lin.

b(4)

NDA 20-947: CMC Deficiencies

| | | | | | | |
|--|--|--|--|--|--|--|
| | | | | | | |
|--|--|--|--|--|--|--|

b(4)

b(4)

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

/s/

Ravi Harapanhalli
12/15/2006 04:44:42 PM
CHEMIST



NDA 20-947

Pennsaid[®] (diclofenac sodium) Topical Solution

Dimethaid International Inc.

Sue-Ching Lin

Review Chemist

**Division of Anti-Inflammatory, Analgesic, and Ophthalmic
Drugs, HFD-550**



Table of Contents

| | |
|---|-----------|
| Chemistry Review Data Sheet..... | 4 |
| The Executive Summary..... | 8 |
| I. RECOMMENDATIONS | 8 |
| A. Recommendation and Conclusion on Approvability | 8 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8 |
| II. SUMMARY OF CHEMISTRY ASSESSMENTS | 8 |
| A. Description of the Drug Product(s) and Drug Substance(s)..... | 8 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation | 9 |
| III. ADMINISTRATIVE..... | 10 |
| A. Reviewer's Signature | 10 |
| B. Endorsement Block | 10 |
| C. CC Block..... | 10 |
| Chemistry Assessment | 11 |
| I. DRUG SUBSTANCE | 11 |
| II. DRUG PRODUCT..... | 13 |
| A. Components/Composition..... | 13 |
| B. Specifications & Methods For Drug Product Ingredients..... | 13 |
| 1. Active Ingredient..... | 13 |
| 2. Inactive Ingredients | 13 |
| C. Manufacturer | 14 |
| D. Methods Of Manufacturing And Packaging | 15 |
| 1. Production Operations | 15 |



Table of Contents

| | |
|---|----|
| 2. In-Process Controls & Tests Adequate..... | 17 |
| 3. Reprocessing Operations..... | 17 |
| E. Regulatory Specifications And Methods For Drug Product | 17 |
| 1. Sampling Procedures..... | 17 |
| 2. Regulatory Specifications And Methods..... | 17 |
| F. Container/Closure System..... | 22 |
| G. Microbiology..... | 24 |
| H. Drug Product Stability..... | 24 |
| 1. Bulk Solution Stability | 24 |
| 2. Photostability Testing..... | 25 |
| 3. Stability Results..... | 26 |
| 4. Stability Protocol..... | 29 |
| III. INVESTIGATIONAL FORMULATIONS | 31 |
| IV. ENVIRONMENTAL ASSESSMENT..... | 31 |
| V. METHODS VALIDATION..... | 32 |
| VI. LABELING..... | 32 |
| VII. ESTABLISHMENT INSPECTION..... | 33 |
| VIII. SUMMARY OF RESPONSES TO THE 12/16/98 FDA IR LETTER..... | 34 |
| IX. LIST OF CHEMISTRY DEFICIENCIES AND COMMENTS (SENT 3/21/02)..... | 39 |
| X. 5/7/02 AMENDMENT IN RESPONSE TO THE DEFICIENCIES ABOVE..... | 41 |



Chemistry Review Data Sheet

1. NDA 20-947
2. REVIEW #: 2
3. REVIEW DATE: 29-July-2002
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> | <u>Document Date</u> |
|------------------------------|----------------------|
| Original submission | 15-Dec-1997 |
| Chemistry Review #1 | 02-May-1998 |
| Withdrawal of NDA by sponsor | 26-Oct-1998 |
| IR letter | 16-Dec-1998 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|----------------------|
| Resubmission | 07-Aug-2001 |
| Amendment (BC) | 13-Feb-2002 |
| Amendment (BC) | 07-May-2002 |

7. NAME & ADDRESS OF APPLICANT:

Name: Dimethaid International Inc.
Address: Los Abedules, Appleby Gardens
St. James, Barbados
Representative: Dr. Frederick N. Ballantyne
10455 North Central Expressway, Suite 109 PMB 320
Dallas, Texas 75231-2213
Telephone: 214-673-0156 (telephone and fax)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pennsaid® Topical Solution
b) Non-Proprietary Name (USAN): diclofenac sodium topical solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Resubmission

10. PHARMACOL. CATEGORY: NSAID

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 1.5% w/w (16 mg/mL)

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: Rx OTC

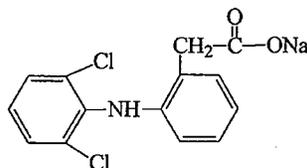
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt



C₁₄H₁₀Cl₂NNaO₂ MW 318.13



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------------|
| | | | | 1 | Adequate | 1/18/02 | |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |
| | | | | 7 | -- | -- | See note below |

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Note: No changes to the original NDA submission have been made to the manufacturers of the packaging system. The _____ composition for each component remain unchanged. Refer to Chemistry Review #1 for the review of the container closure system. Also see page 22 of this review for details.

b(4)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-----------------------------------|
| IND | 42,773 | _____ (diclofenac sodium topical) |

b(4)

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|--|--|-------------|-------------------|
| Biometrics | N/A | | |
| EES | Acceptable | 7/25/02 | S. Adams, HFD-324 |
| Pharm/Tox | N/A | | |
| Biopharm | N/A | | |
| LNC | acceptable | 4/14/98 | Dan Boring |
| Methods Validation | MV was not sent to conserve resources. The applicant did not have a complete MV package until 5/7/02, when the medical officer had decided not to approve the NDA. | | |
| Office of Drug Safety | The proprietary name Pennsaid is acceptable. Some comments about labeling. | 3/12/02 | Nora Roselle |
| EA | categorical exclusion (see review) | | |
| Microbiology | adequate | 2/7/02 | Bryan Riley |



The Chemistry Review for NDA 20-947

The Executive Summary

I. RECOMMENDATIONS

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

The active ingredient is diclofenac sodium, USP. It is manufactured by _____ Detailed CMC information on the drug substance is referenced to DMF _____ which was recently reviewed on 1/18/02 and found to be adequate. The drug substance meets current USP specifications and is tested per USP monograph for diclofenac sodium.

b(4)

(2) Drug Product

Pennsaid[®] Topical Solution contains 1.5% w/w diclofenac sodium as the active ingredient. The drug product also contains 45.5% w/w of dimethyl sulfoxide (DMSO), which was listed as one of the inactive ingredients by the applicant. However, DMSO is known to possess anti-inflammatory activity and is the active ingredient of Rimso[®]-50, an aqueous solution containing 50% w/w of DMSO, which was approved on 4/4/1978 in NDA 17-788.

b(4)

The finished topical solution is packaged in a _____ with a dropper cap and is available in three fill sizes: 15 mL, _____ and 60 mL.



Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Pennsaid[®] is intended to be applied topically _____

b(4)

The applicant proposed an 18-month expiration period for the 15 mL fill size _____
_____ The expiration periods are acceptable based on submitted stability data from three production batches, which include 30 months data under 25°C/60%RH, 18 months data under 30°C/60%RH, and 6 months data under 40°C/75%RH.

b(4)

The recommend storage condition is 25°C (77°F); excursions permitted to 15-30°C.

C. Basis for Approvability or Not-Approval Recommendation

This NDA was first submitted on 12/15/97 and was later withdrawn by the sponsor on 10/26/98. Chemistry review #1 was completed on 5/2/98 and major deficiencies were conveyed to the applicant in an "information request" letter. The 8/7/01 resubmission made major changes to the manufacturing and control of the drug product. In reviewing the resubmission, deficiencies were found by this reviewer and were relayed to the applicant on 3/21/02. These deficiencies involved drug product specification, stability data, post-approval stability protocol, labeling and others. The applicant adequately responded to the deficiencies in the 5/7/02 amendment.

For example, the stability data showed that _____
_____ At this reviewer's request, the structure of the _____

b(4)

diclofenac sodium. The acceptance criterion for this _____
_____ the ICH Guideline (Q3BR) threshold value required for the qualification of impurities.

The applicant did not have a complete methods validation package until 5/7/02. By that time, the medical officer had already decided that the NDA should not be approved due to major clinical deficiencies. This reviewer concluded that it would not be resource efficient to have methods validation performed by the FDA laboratories at this time for a not-approvable NDA. The methods validation packages will be sent to the FDA laboratories if the applicant re-submits this NDA in the future. (According to current CDER policy, the completion of methods validation by the FDA laboratories is not required for determining the approvability of the CMC section.)



Executive Summary Section

III. ADMINISTRATIVE

- A. Reviewer's Signature** N/A
- B. Endorsement Block** N/A
- C. CC Block** N/A

39 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Sue Ching Lin
7/30/02 02:53:15 PM
CHEMIST

John Smith
7/30/02 03:04:54 PM
CHEMIST

11
JUN 1 1998

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-947

REVIEW # 1

DATE REVIEWED: 5/29/98

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| SUBMISSION | 12/15/97 | 12/16/97 | 12/19/97 |
| AR | 1/8/98 | 1/8/98 | |
| AMENDMENT | 1/14/98 | 1/22/98 | 1/27/98 |
| CORRESPONDENCE | 4/24/98 | FAX | 4/24/98 |
| CORRESPONDENCE | 4/29/98 | FAX | 4/29/98 |
| CORRESPONDENCE | 5/1/98 | FAX | 5/4/98 |

NAME & ADDRESS OF APPLICANT: Dimethaid Research Inc.
114 Steelcase Road, West
Markham, Ontario
L3R 3J9

DRUG PRODUCT NAME

Proprietary: Pennsaid™ (1.5% diclofenac sodium topical lotion)
Established: diclofenac sodium
Code Name/#: CAS 15307-79-6
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: NSAID

DOSAGE FORM: lotion

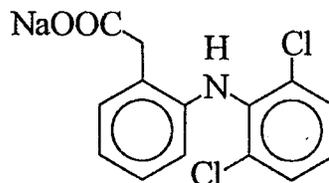
STRENGTHS: 1.5%

ROUTE OF ADMINISTRATION: topical

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-[(2,6-dichlorophenyl)amino] benzenecetic acid monosodium salt C₁₄H₁₀Cl₂NO₂Na 318.13



REMARKS:

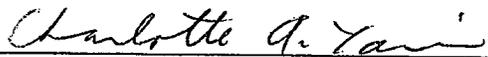
- There is a considerable amount of unnecessary material included in this NDA. Of the 14 "trailer" volumes submitted, the pertinent data is equivalent to 1 volume. The information designated "Used Before June 1, 1997" will not be reviewed. Of the volumes (literally) of chromatographic data supporting the methods, only the summary reports and representative chromatograms will be reviewed.
- The name Pennsaid was found to be acceptable by the Labeling and Nomenclature Committee on 4/14/98.
- Dimethaid has had to change drug product manufacturers after submission of this NDA. They are attempting to make the switch as rapidly as possible.

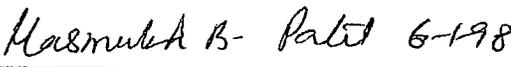
CONCLUSIONS & RECOMMENDATIONS:

This NDA is currently NOT APPROVABLE due to major problems with the stability section, i.e., missing and inconsistent data, and failure to submit information which was requested at the pre-NDA meeting.

cc:

Orig. NDA 20-947
HFD-550/Division File
HFD-550/Chem/Yaciw
HFD-550/CSO/Lutwak
HFD-550/MO/Averbuch
HFD-830/DNDCIII/Chen


Charlotte A. Yaciw, Chemist, HFD-550/830


Hasmukh B. Patel, Chemistry Team Leader HFD-550

filename: n20947c1.rev.doc

21 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process