

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204623Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	PENNSAID (diclofenac sodium topical solution) 2% w/w is for topical use only
Applicant	Mallinckrodt Brand Pharmaceuticals, Inc.
Application/Supplement Number	NDA 204623
Type of Application	Original
Indication(s)	Treatment of the pain of osteoarthritis of the knee(s).
Office/Division	ODE II/DAAAP
Division Project Manager	Mavis Darkwah
Date FDA Received Application	August 7, 2013
Goal Date	February 7, 2014
Date PI Received by SEALD	December 17, 2013
SEALD Review Date	December 18, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is no white space present before the Product Title heading, Boxed Warning and the Indications and Usage heading in HL. Insert white space.*

There is a white space between the HL heading and the HL Limitation Statement. Delete the white space.

Selected Requirements of Prescribing Information

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment: For the product title in HL, since the route of administration is part of the

Selected Requirements of Prescribing Information

nonproprietary name within the parentheses (i.e. diclofenac sodium topical solution), it does not need to be repeated after the parentheses (i.e. “is for topical use only”). We recommend deleting the route of administration after the parentheses.

Consider omitting the strength (2 % w/w) from the product title except if this is a product that is available in multiple strengths. It should be noted that 21 CFR 201.57(a)(2) specifically does not include the product strength as part of the product title. The regulations at 21 CFR 201.57(a)(8) require that the strength appear under the Dosage Forms and Strengths heading in Highlights.

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- NO** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment: *The Boxed Warning heading in HL is not centered. Center it.*

- NO** 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: *The verbatim statement in the Boxed Warning in HL is not centered immediately beneath the heading. Center it.*

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Selected Requirements of Prescribing Information

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Selected Requirements of Prescribing Information

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

***Comment:** The bolded revision date at the end of HL should read as “Revised: December 2013” instead of “Revised: July 2013.”*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.

Comment:

- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should

Selected Requirements of Prescribing Information

be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *There are periods after the numbers for the section headings in the FPI and the TOC. There should be no periods after the numbers for the section headings in the FPI (as shown above) and the TOC. Delete the periods.*

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Comment: *Under subsection 17.8, the cross-reference currently written as [see Use in Specific Populations (8.1) and Impairment of Fertility (13.1)].” should read as “[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)].” i.e. section (not subsection) heading followed by the numerical identifier.*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Selected Requirements of Prescribing Information

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ABIMBOLA O ADEBOWALE
12/18/2013

ERIC R BRODSKY
12/18/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 5, 2013

To: Robert Rappaport, M.D.
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): PENNSAID (diclofenac sodium topical solution) 2% w/w

Dosage Form and Route: for topical use

Application Type/Number: NDA 204623

Applicant: Mallinckrodt Inc.

1 INTRODUCTION

On July 16, 2012, Mallinckrodt Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 204623 for PENNSAID (diclofenac sodium topical solution), 2%, referencing PENNSAID (diclofenac sodium topical solution) 1.5% (NDA 020947). This class 2 resubmission provides for a new dispensing mechanism and a new formulation for PENNSAID (diclofenac sodium topical solution), 2%. On March 4, 2013, Mallinckrodt Inc. received a Complete Response action letter due to Clinical Pharmacology deficiencies. On August 7, 2013, the Applicant resubmitted NDA 204623 in response to the Complete Response (CR) letter with a final bioavailability study report. In addition, the Applicant submitted minor container and carton labeling changes and a safety update that were requested in the CR letter. The proposed indication for PENNSAID (diclofenac sodium topical solution) 2% is for the treatment of the pain of osteoarthritis of the knee(s).

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on September 26, 2013 for DMPP to provide a review of the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for PENNSAID (diclofenac sodium topical solution) 2%.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft PENNSAID (diclofenac sodium topical solution) 2% MG and IFU received on August 7, 2013, and received by DMPP on September 26, 2013.
- Draft PENNSAID (diclofenac sodium topical solution) 2% Prescribing Information (PI) received on August 7, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on November 27, 2013.
- DMPP's review of PENNSAID (diclofenac sodium topical solution) 2% MG and IFU dated February 22, 2013.

3 REVIEW METHODS

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensure that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

15 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NATHAN P CAULK
12/05/2013

BARBARA A FULLER
12/05/2013

LASHAWN M GRIFFITHS
12/05/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 27, 2013

To: Mavis Darwah, Pharm.D.
Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Advertising and Promotional Review I
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204623
OPDP labeling comments for Pennsaid (diclofenac sodium topical solution) 2% w/w

This memo responds to DAAAP's September 26, 2013, consult request, to review the labeling for the Class 2 Resubmission for Pennsaid (diclofenac sodium topical solution) 2% w/w. OPDP has reviewed the version of the draft Prescribing Information (PI) available in the eroom (link sent from Mavis Darwah on November 18, 2013), entitled "NDA 204623 draft-pi 07-2013-FDA revised version 12Nov13_MNK Response.pdf" and the draft Medication Guide and Instructions for use, entitled "Proposed_Pennsaid_draft-pi-07-2013-rev-ver-spnsr-cmmts-word.doc".

We do not have any comments at this time.

If you have any questions regarding the PI, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

Thank you for the opportunity to comment!

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/s/

EUNICE H CHUNG-DAVIES
11/27/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Labeling Review

Date: October 23, 2013

Reviewer: Vicky Borders-Hemphill, PharmD
Division of Medication Error Prevention and Analysis

Acting Team Leader: Morgan Walker, PharmD
Division of Medication Error Prevention and Analysis

Drug Name/Strength: Pennsaid
(diclofenac sodium topical solution 2%)

Application Type/Number: NDA 204623

Applicant/Sponsor: Mallinckrodt Inc.

OSE RCM #: 2013-1823

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Pennsaid (NDA 204623) submitted in response to OSE Review #2012-1119 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On July 16, 2012, the Application for Pennsaid (diclofenac sodium topical solution, 2%) was submitted as a 505(b)(2) to NDA 204623 to propose a new formulation in a new container and closure system, proposed as a metered dose pump. The container label, carton and insert labeling were previously reviewed in OSE Review #2012-1119, dated December 18, 2012. NDA 204623 received a complete response on March 4, 2013, due to the need for a new relative bioavailability study. The Application was resubmitted on August 7, 2013, and included revised container labels, and carton and insert labeling.

2 MATERIALS REVIEWED

DMEPA reviewed the revised container labels and carton labeling submitted by the Applicant on August 7, 2013.

3 CONCLUSIONS

The revised container labels and carton labeling incorporated the recommendations from OSE Review #2012-1119 therefore DMEPA concludes that the revised container labels and carton labeling are acceptable from a medication error perspective.

4 RECOMMENDATIONS

Based on this review, DMEPA has no further recommendations.

If you have further questions or need clarifications, please contact Vaishali Jarral, OSE project manager, at 301-796-4248.

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/s/

BRENDA V BORDERS-HEMPHILL
10/23/2013

MORGAN A WALKER
10/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION			
TO: CDER-DMPP-Patient Labeling Team			FROM: (Name/Title, Office/Division/Phone number of requestor) Mavis Darkwah, Pharm.D. RPM, for: Bob Rappaport, M.D. Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), HFD-170		
REQUEST DATE: September 25, 2013		NDA/BLA NO.: 204623	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW) New NDA/Class 2 resubmission		
NAME OF DRUG: diclofenac sodium topical solution 2% w/w	PRIORITY CONSIDERATION: priority	CLASSIFICATION OF DRUG: Analgesic	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) 11/24/13		
SPONSOR: Mallinckrodt Inc.			PDUFA Date: February 07, 2014		
TYPE OF LABEL TO REVIEW					
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION	
EDR link to submission: EDR Location: \\CDSESUB1\evsprod\NDA204623\204623.enx EDR Location: \\CDSESUB1\evsprod\NDA204623\0025					
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.					
COMMENTS/SPECIAL INSTRUCTIONS: The Division received a class 2 resubmission for diclofenac sodium topical solution 2% w/w. This is a 505(b)(2) application referencing Pennsaid (diclofenac sodium topical solution) 1.5% w/w (NDA 020947) . Request to evaluate the adequacy of the Med guide and Instruction for Use. Additionally, please evaluate the IFU for the pump device. Filing/Planning Meeting: September 19, 2013 Mid-Cycle Meeting: November 7, 2013 Labeling Meetings: TBD Wrap-Up Meeting: January 9, 2014					

Contact Mavis Darkwah, RPM (2-3158) if you have questions or need additional information.

SIGNATURE OF REQUESTER
Mavis Darkwah, Pharm.D., RPM

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
 eMAIL (BLAs Only) DARRTS

Version: 12/9/2011

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/s/

MAVIS Y DARKWAH
09/26/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion (DCDP)**

******Pre-decisional Agency Information******

Memorandum

Date: February 27, 2013

To: Swati Patwardhan, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer, DCDP

CC: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 204623
DCDP labeling comments for Diclofenac sodium (diclofenac sodium
topical solution), 2%
Medication Guide

DCDP has reviewed the Medication Guide (Med Guide) for Diclofenac sodium (diclofenac sodium topical solution), 2% (Diclofenac sodium) that was submitted for consult on June 6, 2012.

DCDP's comments on the proposed Medication Guide are based on the proposed draft marked version of the Medication Guide provided by LaTonia Ford (DMPP) on February 22, 2013. DMPP's review of the Medication Guide is being provided to the Review Division under separate cover.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
02/27/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 22, 2013

To: Bob A. Rappaport, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Latonia Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)
and Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route: Diclofenac sodium topical solution, 2%
(diclofenac sodium topical solution)

Application Type/Number: NDA 204623

Applicant: Mallinckrodt Inc.

1 INTRODUCTION

On May 4, 2012, Mallinckrodt Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) to their approved New Drug Application (NDA) 20-947/S-009 for PENNSAID (diclofenac sodium topical solution) 1.5%. This PAS provides for diclofenac sodium topical solution as a 2% topical solution in a metered-dose pump.

On July 16, 2012, the Agency determined that the proposed PENNSAID product was a new product because it uses a new dispensing mechanism and has a new formulation. As requested by the Agency, Mallinckrodt resubmitted NDA 20947/S-009 as an original 505(b)(2) New Drug Application 204623 for diclofenac sodium topical solution, 2% (diclofenac sodium topical solution).

The proposed indication for diclofenac sodium topical solution, 2% is for the treatment of the pain of osteoarthritis of the knee(s). Diclofenac sodium topical solution, 2% was developed based on PENNSAID (diclofenac sodium topical solution) 1.5% which was approved in November 2009, for the treatment of signs and symptoms of osteoarthritis of the knee(s). The Applicant's rationale for diclofenac sodium topical solution, 2% is that it will reduce the dosing frequency from four times daily to twice daily.

On June 6, 2012, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for diclofenac sodium topical solution, 2% (diclofenac sodium topical solution).

This review is written in response to a request by DAAAP for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for diclofenac sodium topical solution, 2% (diclofenac sodium topical solution).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft diclofenac sodium topical solution, 2% (diclofenac sodium topical solution) Medication Guide (MG) and Instructions for Use (IFU) received May 4, 2012 revised by the Review Division throughout the review cycle, and received by DMPP on February 13, 2013.
- Draft diclofenac sodium topical solution, 2% (diclofenac sodium topical solution) Medication Guide (MG) and Instructions for Use (IFU) Prescribing Information (PI) received on May 4, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on February 13, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
02/22/2013

BARBARA A FULLER
02/22/2013

LASHAWN M GRIFFITHS
02/22/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 22, 2013

To: Swati Patwardhan
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: L. Shenee' Toombs, Pharm.D., Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 204623
DPDP labeling comments for diclofenac sodium topical solution, 2%

In response to DAAAP's June 6, 2012, consult request, DPDP has reviewed the draft Prescribing Information (PI) for diclofenac sodium topical solution, 2%. Comments on the proposed PI are based on the version sent via email from Swati Patwardhan (RPM) on February 13, 2013, entitled "NDA 204623 draft-pi-FDA version Feb 11-2013_MNK response." Please note that DPDP's comments on the proposed PI are provided directly on the marked version below.

If you have any questions regarding the package insert, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov.

Thank you for the opportunity to comment!

Enclosure: Marked up PI

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/s/

EUNICE H CHUNG-DAVIES
02/22/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 18, 2012

TO: Robert A. Rappaport, M.D.
Director,
Division of Anesthesia, Analgesia, and Addiction
Products
Office of Drug Evaluation II

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Review of EIRs covering NDA 204623, PENNSAID**
(Diclofenac Sodium) Solution, sponsored by
Mallinckrodt, Inc., Hazelwood, Missouri

At the request of the Division of Anesthesia, Analgesia, and Addiction Products, the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted audits of the clinical and analytical portions for the following bioequivalence studies.

Study #1: COV05100175

Study Title: "A phase-I, randomized, single center, open-label, multiple-dose, two-way crossover study to evaluate the pharmacokinetics, bioavailability, and safety of PENNSAID VISCOUS (Diclofenac Sodium Topical Solution) 2.0% w/w in comparison to PENNSAID® (Diclofenac Sodium Topical Solution 1.5% w/w in healthy subjects"

Study #2: COV05100070

Study Title: "A phase-I, randomized, single center, open-label, multiple-dose, three-way crossover study to evaluate the pharmacokinetics, bioavailability, and safety of PENNSAID (Diclofenac Sodium topical solution) Gel 2.0% w/w in comparison with Sandoz 75 mg Diclofenac Sodium Delayed-Release tablet and PENNSAID® (Diclofenac Sodium Topical Solution) in healthy volunteers"

The objectives of the inspected studies were to (1) compare the pharmacokinetics of PENNSAID (Diclofenac Sodium topical Solution) 2.0% w/w with PENNSAID® (Diclofenac Sodium Topical Solution) 1.5% w/w; (2) compare the pharmacokinetics of PENNSAID (Diclofenac Sodium topical solution) 2.0% w/w with Sandoz 75 mg Diclofenac Sodium delayed-release tablets; and 3) evaluate the safety and tolerability of PENNSAID (Diclofenac Sodium topical solution) 2.0% w/w in healthy volunteers.

The FDA audit of the analytical portion of study COV05100070 was conducted at [REDACTED] (b) (4) by ORA investigator [REDACTED] (b) (4) and OSI scientist Jyoti Patel. The FDA audit of the analytical portion of study COV05100175 was conducted at [REDACTED] (b) (4) by ORA investigator [REDACTED] (b) (4) and OSI scientist Gopa Biswas. The FDA audit of the clinical portions of studies COV05100070 and COV05100175 was conducted at Comprehensive Clinical Development, Inc., Miramar, FL (November 28 - December 12, 2012) by ORA investigator Ethan P. Stegman (Florida District Office) The audits included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firms' management and staff.

Following the inspections of the analytical portions of the above two studies, **no significant objectionable conditions were observed at either analytical site and no Form FDA-483 was issued; however, Form FDA-483 (Attachment 1) was issued at the clinical site.** The Form FDA-483 observation for studies COV05100070 and COV05100175 and OSI's evaluation of the observation follow:

Comprehensive Clinical Development, Inc., Miramar, FL:

1. **Samples of the test article and reference standard used in a bioavailability study were not retained. Specifically, firm**

management stated that they did not retain samples for Protocol COV05100070 and Protocol COV05100175.

The firm acknowledged that reserve samples were not retained (**Attachment 2**). Corrective actions will be taken to prevent such incidences in future.

Evaluation:

The reserve samples (required by 21 CFR 320.38) were not retained at the clinical site. Thus, no reserve samples were available at the time of inspection. As a result, the authenticity of the test and reference drug products used in studies COV05100070 and COV05100175 cannot be confirmed at Comprehensive Clinical Development, Inc., Miramar, FL.

Conclusion:

Following the inspections of the analytical and clinical portions of studies COV05100070 and COV05100175, OSI reviewers have the following recommendations:

- For the analytical portions of the studies, no objectionable conditions were observed.
- For the clinical portions of the studies: due to the lack of reserve samples, the authenticity of the test and reference drug products administered at Comprehensive Clinical Development, Inc., Miramar, FL cannot be confirmed. Therefore, data cannot be accepted for further agency's review.

Jyoti B. Patel, Ph.D.
Gopa Biswas, Ph.D.
Bioequivalence Branch,
DBGLPC, OSI

Classifications:

OAI: Comprehensive Clinical Development, Inc., Miramar, FL.

FEI: 3006116374

NAI: [REDACTED] (b) (4)

NAI: [REDACTED] (b) (4)

Page 4 of 4- NDA 204623, PENNSAID (Diclofenac Sodium topical solution) 2% w/w

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Patel/Biswas/Cho/Dejernett/CF

OND/ODEII/DAAAP/Patwardhan/Rappaport, Robert A.

HFR-CE250/Smith (DIB)/Harris (BIMO)

HFR-SE250/Sinninger (DIB)/Torres (BIMO)

HFR-SE2590/Stegman, Ethan

HFR-CE850/Bigham (DIB)/Matson (BIMO)

HFR-CE8590/Richard-Math (BIMO)/Burosh, Denise

Draft: JBP 12/17/2012

Edit: SC 12/17/2012; SHH 12/18/2012

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FACTS: 1435595

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB

ATTACHMENTS:

Attachment 1: Form FDA-483 (Comprehensive Clinical Development, Inc., Miramar, FL)

Attachment 2: Acknowledgement from (Comprehensive Clinical Development, Inc., Miramar, FL)

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/s/

JYOTI B PATEL
12/18/2012

SAM H HAIDAR
12/19/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 18, 2012

Reviewer: Anne Crandall Tobenkin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Deputy Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s): Pennsaid (Diclofenac Sodium) Topical Solution

Strength(s): 2 %

Application Type/Number: NDA 204623

Applicant/sponsor: Mallinckrodt

OSE RCM #: 2012-1119

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed Pennsaid container label, carton and insert labeling for Pennsaid (b) (4) (NDA 204263) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Pennsaid was first approved in November, 2009 as a topical solution is dosed as 40 drops to the knee(s) four times daily. Pennsaid was evaluated in a 915 review which identified medication errors associated with wrong route and wrong dose. Subsequent to this review, the Pennsaid labels and labeling of the currently marketed product were revised to address these errors and also submitted a supplement on May 1, 2012 proposing a new formulation and product design. (b) (4)

1.2 REGULATORY HISTORY

On July 16, 2012, the Agency determined that the proposed Pennsaid product is a new NDA (204623), rather than a supplement to the previous NDA (020947) because this product not only uses a new dispensing mechanism, but is also a new formulation. During this time, DMEPA evaluated the proposed name, Pennsaid (b) (4), which was proposed by the Applicant. DMEPA determined that the modifier, (b) (4) was unnecessary and did not convey the difference between the proposed Pennsaid and the currently marketed Pennsaid product. This was conveyed to the applicant during a teleconference with the Agency and Mallinckrodt on July 26, 2012. Mallinckrodt agreed to withdraw the proposed name.

1.2 PRODUCT INFORMATION

Table 1: The following product information is provided in the May 4, 2012 proprietary name submission.

Product Characteristics	Proposed Pennsaid (NDA 204623)	Pennsaid (NDA 020947)
Active Ingredient	Diclofenac Sodium	Diclofenac Sodium
Indication of Use	Osteoarthritis of the knee	Osteoarthritis of the knee
Route of Administration	Topical	Topical
Dosage Form	Solution	Solution
Strength	2%	1.5%
Dose and Frequency	2 pumps twice daily to affected knee(s)	40 drops four times daily to affected knee(s)
How Supplied	112 mL bottle	150 mL bottle and 15 mL (sample) bottle

Product Characteristics	Proposed Pennsaid (NDA 204623)	Pennsaid (NDA 020947)
Storage	Room temperature	Room temperature
Container and Closure Systems	112 mL bottle fitted with a 1 mL metering pump for a multi-dose container closure system. It does not appear to be child-resistant.	15 mL and 150 mL HDPE bottles with a dropper spout cap. Bottles are not child-resistant.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Pennsaid medication error reports. We also reviewed the Pennsaid labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2.

Table 2: FAERS Search Strategy	
Date	October 18, 2011 (date of last Medication Error search using AERS database) to August 27, 2012
Drug Names	Pennsaid (trade name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified nine cases. Each case was reviewed for relevancy and duplication. After individual review, six cases were not included in the final analysis because the cases involved adverse events associated with a drug product other than Pennsaid or an adverse event occurred that was not associated with a Pennsaid medication error.

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted May 4, 2012(Appendix A)
- Carton Labeling submitted May 4, 2012 (Appendix B)
- Insert Labeling submitted May 4, 2012 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Pennsaid labels in OSE reviews: # 02-0010, # 2009-427, and # 2011-3901. We re-examined the reviews and ensured all our previous recommendations were implemented.

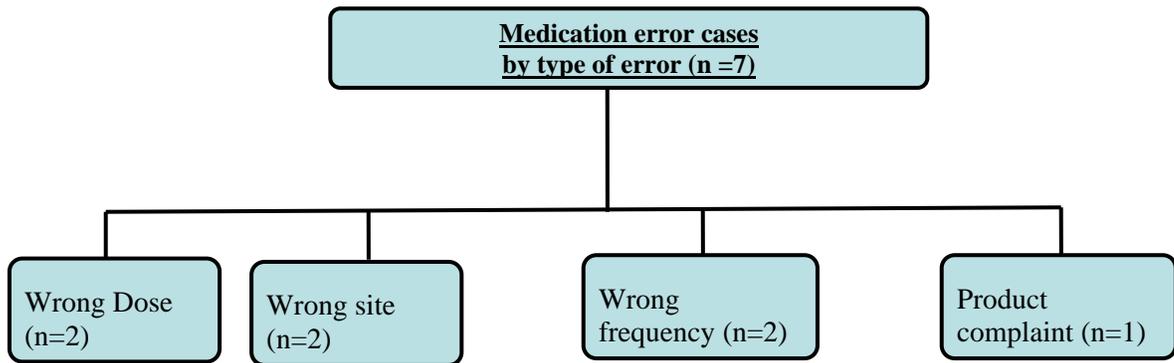
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Pennsaid product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, three Pennsaid medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error. Two of the cases describe three different types of medication errors, hence the number of errors exceed the number of cases. Appendix C provides listings of all ISR numbers and case narratives for the cases summarized in this review.

Figure 1: Pennsaid medication error cases categorized by type of error (n =7)



² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

- **Wrong Dose (n=2)**

In both cases the patient used less than the recommended dose. One case states the physician prescribed 40 drops however the patient utilized less than prescribed. The second case describes the patient using only two drops. No causality was reported in either of the cases for the wrong dose used.

- **Wrong Site (n=2)**

Two cases described wrong site application for Pennsaid. One case states that the physician prescribed Pennsaid for “chest muscle tightness” which is an unapproved use of Pennsaid. The other case describes a patient using another patient’s Pennsaid for application to the knuckles. No adverse events occurred as a result of the errors.

- **Wrong Frequency (n=2)**

One case describes the physician prescribing Pennsaid four times daily; however the patient applied the product twice daily. The other case describes the patient applying Pennsaid to her knuckles as needed, however the case did not describe how often it was needed or applied. No adverse events were described as a result of the wrong frequency.

- **Product Quality Complaint (n=1)**

One case is a product quality complaint, describing the product as “runs off the leg and is not working”. The patient used the product as prescribed, 40 drops to the knee four times daily; however the patient had difficulty applying the required amount of product for the prescribed dose to the knee area.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Pennsaid is currently marketed as a single strength, 1.5% topical solution that requires 40 drops applied to the affected knee(s) four times daily. The proposed Pennsaid product is supplied in a pump dispenser and is a 2% topical solution, which is applied twice daily. Possible confusion between the two products can result in overdose or underdose. (b) (4)

Because the revised product decreases both the dose and frequency, the proposed container label, carton and insert labeling should highlight these important differences between the two products. Additionally, the 2% strength can be highlighted to increase awareness of the increased strength. The two container labels and carton labeling were compared to ensure that there is adequate differentiation between the two products so that if both Pennsaid products are co-marketed (b) (4) confusion will be unlikely from a similar appearance.

However, due to the cases of wrong dose, wrong site, and wrong frequency for the currently marketed product, the proposed product should display the dosing and application instructions prominently on the container label and carton labeling. The current Pennsaid container label and carton labeling does state to use only on the knee, however it is located on the back panel and is not prominent. The proposed Pennsaid product also includes the instructions for application to the knee along with the dose and

frequency; however it is not prominently displayed. More prominent display of instructions for correct use can better convey the instructions to help mitigate these errors.

Moreover, the insert labeling references a dose of (b) (4). However, this reference does not provide practitioners a reference to the milligram dose of diclofenac sodium. In addition, the product is not designed to have the patient measure or verify a specific volume of solution was delivered by the pump. A review of Axiron (testosterone) topical solution insert labeling, a product that also delivers a dose via a pump, indicates that the dose is referred to in milligrams followed by a reference to a pump and or activation. Thus, it also seems appropriate to indicate a milligram dose for this product to help provide a better dosing reference for practitioners. Although it also seems appropriate to provide dosing references in terms of pumps or activations as general dosing information for patients provided the practitioners understands how many milligrams is contained in each pump.

Additionally since the currently approved Pennsaid product is a solution, product quality complaints are likely due to the runny nature of this product and the large number of drops required per dose, in addition, the application site, which is not flat. This type of complaint will likely be mitigated by the increased viscosity of the proposed Pennsaid product and also the decreased amount (40 drops vs. 2 pumps) of product needed to apply for each dose. Additionally, the pump dispenser will make dosing easier by measuring the dose of two pumps of Pennsaid rather than the patient having to count up to 40 drops and applying 10 drops in separate intervals. Furthermore, the proposed product should mitigate previously identified medication errors not found during this search; including patients using Pennsaid in the eye (refer to OSE Review 2011-3901). The proposed pump bottle is unlikely to get confused with an eye product prompting patients to apply to the wrong site.

4 CONCLUSIONS

DMEPA concludes that the proposed product design is an improvement to the currently marketed Pennsaid product because it requires the application of two pumps (as opposed to 40 drops) and is applied less frequently thereby improving patient compliance. The proposed pump design is also less error prone because it utilizes a pump system which dispenses a metered amount of medication instead of relying on the patient to keep track of the amount dispensed.

However, the Pennsaid 2% container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and to mitigate confusion with the currently marketed Pennsaid product.

5 RECOMMENDATIONS

DMEPA provides the following comments for consideration by the review division prior to approval of this NDA:

5.1 COMMENTS TO THE DIVISION

A. INSERT LABELING

1. The Highlights and Dosage and Administration Section list a (b) (4) dose followed by a reference to 2 pumps in parenthesis, “(b) (4) (2 pumps)”. We recommend elimination of a volumetric dosing reference, because it does not provide practitioners with an equivalent milligram dose and practitioners should not prescribe a (b) (4) dose. The product is not designed for patients to measure or verify (b) (4) were actually delivered by the pump. Thus, we recommend replacing the (b) (4) dose designation with an actual milligram dose followed by the number of pump activations similar to “40 (b) (4) mg (2 pump activations)”.
2. We recommend revising the Dosage and Administration Section statement that reads in part “Dispense 2 pumps of Pennsaid ...” to read “Dispense 40 (b) (4) mg (2 pump activations) of Pennsaid ...”.
3. Although we recommended incorporation of an actual milligram dose for practitioners, it also seems appropriate to provide dosing references in terms of pumps or activations for patients. Thus, we are not recommending incorporating the milligram dose in the usual dosage statement that will appear on the container label and carton labeling.

5.2 COMMENTS TO THE APPLICANT

We acknowledge that the proposed proprietary name has not been granted; therefore, we are providing preliminary comments regarding the presentation of the proposed proprietary name on your current labels and labeling.

A. CONTAINER LABEL

1. Revise the proprietary name, active ingredient, and strength statement on the principal display panel so that it appears horizontally oriented (rather than vertical) in order to improve the readability of this important information by standardizing the orientation of the product information. This information should be presented in the same orientation in which the product will typically be stored by patients.
2. Ensure that the established name is ½ the size and prominence of the proprietary name so that it is in accordance with CFR 201.10(g)(2). Additionally, ensure that the proprietary name is presented in the same color and font. Finally, present the double letters “nn” in Pennsaid in regular font. As currently presented it may be confused with the letters “m” or “w”.
3. Increase the prominence of the strength statement, “2%” by increasing the font size or some other methods to help further differentiate the proposed Pennsaid product from the currently marketed Pennsaid product, which is 1.5%.

4. Unbold the NDC number and the volume statement so that it is less prominent than other important safety information. Also, relocate the volume statement so that it appears away from the NDC number (e.g. on the bottom part of the principal display panel).
5. Revise the “(b) (4) contains...” statement to read “Each activation delivers 20 (b) (4) mg of diclofenac sodium.”
6. Remove the “Avoid contact with the eyes or mucous membranes” statement in order to decrease clutter on the principal display panel. If space permits, this statement could be relocated to the back panel.
7. Remove all the instructions from “Apply Pennsaid (b) (4)” to “After application...” from the back panel to decrease the clutter on the label.
8. Revise the usual dose statement from “(b) (4) : “Apply two pump activations to affected knee(s) two times a day”. This format helps highlight that the product may be applied to one or both knees.
9. Remove the color block that surrounds “Mallinckrodt” so that attention is not diverted from important safety information such as name, strength, and Medication Guide statements.

B. Carton Labeling

1. See Comments A2, A3 and A8.
2. Revise the “(b) (4) ...” statement to read “Each pump activation delivers 20 (b) (4) mg of diclofenac sodium.” Relocate the statement to appear on the side panel where the “Rx only” statement currently appears.
3. Remove the “Rx only” statement on the side panel because it appears on both the front and the back panel.
4. Relocate the “Avoid contact with the eyes or mucous membranes” statement to the side panel so that it appears beneath the instructions for use and decreases clutter on the principal display panel.
5. Relocate the “For External Use Only” statement so that it appears in the highlighted area of the front and back panel above the “Usual Dosage:...” statement. Also increase the font size of the Usual Dosage statement to ensure that the directions for use are highly visible to ensure that patients and practitioners understand that the directions for use for the proposed Pennsaid product are different compared to the currently marketed product.

If you have further questions or need clarifications, please contact Teena Thomas, project manager, at 301-796-0549.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Container Labels



6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CARLOS M MENA-GRILLASCA on behalf of ANNE C TOBENKIN
12/18/2012

SCOTT M DALLAS on behalf of LUBNA A MERCHANT
12/18/2012

SCOTT M DALLAS
12/18/2012

CAROL A HOLQUIST
12/18/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204623 BLA#	NDA Supplement #: BLA Supplement #	Efficacy Supplement Type
Proprietary Name: Pennsaid (b) (4) Established/Proper Name: diclofenac sodium Dosage Form: Topical Solution, metered Strengths: 2%		
Applicant: Mallinckrodt Inc. Agent for Applicant (if applicable): NA		
Date of Application: May 4, 2012 (although submitted on July 13, 2012, the receipt date was back-dated to May 4, 2012. See July 16, 2012, memo to file in DAARTS) Date of Receipt: May 4, 2012 Date clock started after UN: NA		
PDUFA Goal Date: March 4, 2013 (Monday)		Action Goal Date (if different):
Filing Date: July 3, 2012		Date of Filing Meeting: June 15, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3, new Dosage form		
Proposed indication(s)/Proposed change(s): proposes a 2% w/w topical solution, metered for treatment of (b) (4) OA for knees with dosing frequency of twice day application		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1)	<input checked="" type="checkbox"/> 505(b)(2)
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1)	<input type="checkbox"/> -505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<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 is Priority.</i>	<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"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<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 (<i>if OTC product</i>):				
List referenced IND Number(s): 075045				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			✓	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid * <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required * Half user fee paid on 5/3/2012, second half paid on 7/5/2012			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			✓		
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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			✓		
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)]?			✓		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
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.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<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 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>			✓		

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
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<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		✓		
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	✓			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		✓		
<p>If yes, 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>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" 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>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	✓			(b) (4) contains language “ to the best

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>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...”</i></p>				<p>of my knowledge...” (pg.14/sec.1.3.3</p> <p>The main overall certification from Mallinckrodt is acceptable</p>
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</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>			✓	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			✓	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></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>	✓			New dosing Regimen. Applicant has requested a full waiver., as the condition of OA is rare in pediatric population.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	✓			Full waiver requested

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	✓			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	✓			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		✓		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	✓			proprietary name submitted as separate submission
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>			✓	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		✓		None at this time
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): September 25, 2006 <i>If yes, distribute minutes before filing meeting</i>	✓			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		✓		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): August 28, 2008	✓			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 15, 2012

BLA/NDA/Supp #: 204623

PROPRIETARY NAME: Pennsaid (b) (4)

ESTABLISHED/PROPER NAME: diclofenac sodium

DOSAGE FORM/STRENGTH: Topical Solution, metered, 2% w/w

APPLICANT: Mallinckrodt Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: This NDA proposes 2% w/w topical solution metered for the treatment (b) (4) (b) (4) of osteoarthritis (OA) of the knee. The dosing frequency will be twice daily (BID). A new trade name of “Pennsaid (b) (4)” is proposed. A meeting request was submitted in August 2006, to discuss the 2% new formulation under IND 075045.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Swati Patwardhan	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Jacqueline A. Spaulding	Y
	TL:	Frank Pucino*	Y
Social Scientist Review (for OTC products)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (for OTC products)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (for antimicrobial products)	Reviewer:	NA	
	TL:	NA	

Clinical Pharmacology	Reviewer:	Ying Fan	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Feng Li	N
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jay Chang	Y
	TL:	Adam Wasserman	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Kris Raman	Y
	TL:	Ramesh Raghavachari	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	NA	
	TL:	NA	
CMC Labeling Review	Reviewer:	Kris Raman	Y
	TL:	James Vidra	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Anne Tobenkin	N
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:	NA	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:	NA	
Bioresearch Monitoring (OSI)	Reviewer:	NA	

	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:	NA	
Other reviewers			
Other attendees	Bob Rappaport Matt Sullivan		Y Y

* As of June 26, 2012, Ellen Fields is the Medical TL

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues: did not identify RLD product but ANDA products (should be asked to identify RLD under relevant NDA)</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input 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? <p>If no, explain:</p>	<input checked="" 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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: the application did not raise significant safety or efficacy issues

<ul style="list-style-type: none"> ○ <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> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <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
<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> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</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
<p>IMMUNOGENICITY (BLAs/BLA efficacy)</p>	<input checked="" type="checkbox"/> Not Applicable

<p>supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <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 type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></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

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob Rappaport 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Not attached Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input type="checkbox"/>	
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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/

SWATI A PATWARDHAN
07/17/2012

SARA E STRADLEY
07/17/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 204623

Application Type: New Drug Application

Name of Drug: Pennsaid (diclofenac sodium) Topical Solution, metered 2%

Applicant: Mallinckrodt, Inc.

Submission Date: May 4, 2012

Receipt Date: May 4, 2012

1.0 Regulatory History and Applicant's Main Proposals

The NDA proposes a 2% w/w topical solution, metered for treatment (b) (4) of OA for knees with dosing frequency of twice day application. In September 2006, Nuvo Research (the then-Sponsor) had a Pre-IND meeting with DAAAP to discuss the new 2% formulation. (b) (4)

(b) (4)
Nuvo Research Inc. then transferred the ownership of IND 075045 to Mallinckrodt Inc. in June 2009. On May 10, 2010, Mallinckrodt, Inc. submitted IND 75045 to conduct a Phase 2 study of PENNSAID Gel as the initial study. (b) (4)

On May 4, 2012, Mallinckrodt submitted an efficacy supplement to add 2 % formulation as new strength under NDA 20947. In this supplement, Mallinckrodt states that subsequent evaluation and rheology study has established that 2 % formulation is not a new dosage form, but a topical solution. Subsequent discussion with User fee staff and Orange book staff concluded it to be a new dosage form due to the labeling claim of the pump. The label claims that the pump will deliver exactly 1 mL of drug and only 2 pumps should be used per dose, which results into a new dosage form. Mallinckrodt resubmitted the May 4, 2012, submission under new NDA 204623 on July 13, 2012. From the review clock perspective, the PDUFA goal will not be affected and will be March 4, 2013.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

RPM PLR Format Review of the Prescribing Information

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 7, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *No waiver has been granted. The Highlight section seems to be longer than half page*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *None*

- NO** 4. White space must be present before each major, the heading in HL.

Comment: *All major Headings do not have white space in between.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Not all statements meet this criterion (see Dosage & Admin, bullets 3,4,5, and 7)*

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *RMC Heading is not present*

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *None*

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment: *None*

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *None*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment: *None*

Initial U.S. Approval

Selected Requirements of Prescribing Information (SRPI)

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: None

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment: None

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment: None

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment: None

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment: None

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment: None

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment: None

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment: None

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment: None

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: None

Indications and Usage

YES

Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: *Product is an NSAID*

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *Only Solution*

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment: *None*

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *None*

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *None*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *Has 3rd bullet*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *In “Month Year” format*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Selected Requirements of Prescribing Information (SRPI)

Comment: None

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.

Comment: There is an “” symbol after the word “CONTENTS”*

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: None

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: None

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment: None

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment: None

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment: None

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**

Comment: None

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.

Comment: None

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment: None

- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Selected Requirements of Prescribing Information (SRPI)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Sec. 12.4 is listed as “platelets” in the draft PI instead of Microbiology. SEALD will be consulted at later date to provide an input on the acceptability.

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: Medication Guide and Patient Instructions for Use is included as subsection 17.10 and section 17.11, respectively, under Section 1.

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: None

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: None

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment: None

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information (SRPI)

Comment: None

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment: None

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment: None

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment: None

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: The statement reads as “See FDA-Approved Medication Guide (17.10) for specific patient instructions.”

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/s/

SWATI A PATWARDHAN
07/17/2012

SARA E STRADLEY
07/17/2012