CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204623Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204623/000	**Sponsor:**	MALLINCKRODT INC
Org. C	170		675 MCDONNELL BLVD
Priority:	3		HAZELWOOD, MO 63042
Stamp Date:	04-MAY-2012	**Brand Name:**	DICLOFENAC SODIUM
PDUFA Date:	04-MAR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	DICLOFENAC SODIUM
District Goal:	03-JAN-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION; DICLOFENAC SODIUM; 2%	

FDA Contacts:	L. RIVERA	Project Manager	3017964013
	D. CHRISTODOULOU	Team Leader	3017961342

Overall Recommendation:	ACCEPTABLE	on 31-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 23-OCT-2012	by EES_PROD		
	PENDING	on 21-AUG-2012	by EES_PROD		
	PENDING	on 02-AUG-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Reference ID: 3445226

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9617231 **FEI:** 3006616345

ESTEVE QUIMICA
KM 5 ROAD TP 2125

TARRAGONA, , SPAIN

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-AUG-2012

Decis ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3445226

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-NOV-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9615349 **FEI:** 3003242976

NUVO MANUFACTURING
3655 CHEMIN DE LA COTE BISSONNETTE

VARENNES, QUEBEC, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE STABILITY TESTER

Profile. (b) (4)) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3445226

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: Feb 8, 2013

FROM: Yong Hu, Ph.D.

SUBJECT: Addendum to CMC Review #1 of NDA 204623 for Diclofenac Sodium Topical Solution 2% w/w
Applicant: Mallinckrodt

TO: NDA 204623 file

This is a follow up to CMC Review #1 for the purpose of indicating resolution of the CMC issues (b) (4) (b) (4) (b) (4) and also indicating the final recommendation from the Office of Compliance regarding the manufacturing and testing facilities.

The comments in the CMC Review #1 about the (b) (4) deficiencies are provided below together with the applicant's responses in the amendment dated 2/4/2013.

(b) (4)

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

3 Pages have been Withheld As A Duplicate Copy of the EES Summary Report dated 02/08/2013 Previously in this Section of the Approval Package

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

/s/

YONG HU
02/08/2013

PRASAD PERI
02/08/2013
I concur

NDA 204623

Diclofenac Sodium Topical Solution, 2% w/w

Mallinckrodt Inc.

Yong Hu, Ph.D.

Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

For

Division of Anesthesia, Analgesia, and Addiction Products

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Chemistry Review Data Sheet

1. NDA: 204623

2. REVIEW #: 1

3. REVIEW DATE: 1/26/2013

4. REVIEWER: Yong Hu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	5/4/2012
Response to filing comments	8/22/2012
Quality/Response to Information Request	9/21/2012
Response to Information Requests	Emailed to PM Luz Rivera on 1/24/2013. Official submission to follow.

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc.
Address:	Mallinckrodt Inc. (30-2) 675 McDonnell Blvd. Hazelwood, MO 63042
Representative:	Bunny Bierman, Manager Regulatory Affairs
Telephone:	314-654-8048

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not submitted yet.
b) Non-Proprietary Name (USAN): Diclofenac sodium topical solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

Reference ID: 3254049

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 b(2); The reference drug is Pennsaid (diclofenac sodium) topical solution 1.5% (NDA 20947), which Mallinckrodt is also the applicant for.

10. PHARMACOL. CATEGORY:

Anti-inflammatory agent.

11. DOSAGE FORM:

Solution.

12. STRENGTH/POTENCY:

2% w/w.

13. ROUTE OF ADMINISTRATION:

Topical.

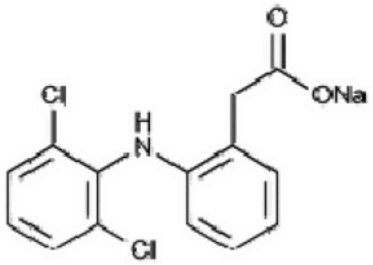
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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



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

Molecular formula: $C_{14}H_{10}Cl_2NNaO_2$
Molecular weight: 318.13

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	Esteve Quimica, S.A.	Active Ingredient	1	Adequate	6/20/2012	
	III	(b) (4)	(b) (4)	4	N/A		Also referenced by another approved product
	III			4	N/A		Also referenced by another approved product
	III			1	Adequate	5/23/2008	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75045	IND supporting the NDA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending.		
Pharm/Tox	The extractables [redacted] (b) (4) and [redacted] (b) (4) from the container closure are not of safety concern. The impurity limits for the drug product are acceptable.	Email communications.	Dr. Jay Chang
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A.		
OPDRA	N/A.		
EA	N/A. Categorical exclusion acceptable to this reviewer.		
Microbiology	The pharmaceutical development data (product formulation, bioburden results, antimicrobial effectiveness testing results and [redacted] (b) (4)) indicate that microbial testing is not necessary for this product.	8/29/2012	Email communication from Dr. Bryan Riley (see attached email).

Reference ID: 3254049

The Chemistry Review for NDA 202450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable from CMC perspective, pending the applicant's satisfactory revision of [redacted] (b) (4) and overall recommendation from the Office of Compliance regarding the GMP status of the manufacturing and testing facilities.

[redacted] (b) (4) The deficiency comments [redacted] (b) (4) have been included at the end of this review and can be addressed by the applicant in a short timeframe. The deficiency [redacted] (b) (4) does not compromise the adequacy of the proposed to-be-marketed multi-dose product. When the deficiencies are addressed by the applicant, an addendum to this review will be provided by this reviewer.

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

None.

II. Summary of Chemistry Assessments

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

The diclofenac sodium topical solution 2% w/w, which is to be administered twice daily, is an improved product over the FDA-approved PENNSAID (diclofenac sodium) topical solution 1.5% w/w, which requires QID dosing. In addition, the diclofenac sodium topical solution 2% w/w is provided in a metered-dose container, providing better dosing accuracy and patient compliance. Compared to the PENNSAID (diclofenac sodium) topical solution 1.5%, the formulation composition of the 2% topical solution includes the same concentration of dimethyl sulfoxide (45.5% w/w), [redacted] (b) (4) propylene glycol [redacted] (b) (4) and [redacted] (b) (4) ethanol 95% [redacted] (b) (4). The marketed PENNSAID solution 1.5% w/w formulation utilizes glycerin ([redacted] (b) (4) whereas hydroxypropyl cellulose (HPC) [redacted] (b) (4) for the 2% formulation. [redacted] (b) (4) higher product viscosity which facilitates more convenient product application. Also, [redacted] (b) (4) ethanol concentration in the 2% formulation reduces drying time at the application site so that the drug product stays where it is applied.

Reference ID: 3254049

The manufacturer of the drug product is Nuvo Manufacturing, a Division of Nuvo Research Inc. in Varennes, Quebec, Canada. The manufacturing process is [redacted] (b) (4)

The container closure system is the [redacted] (b) (4) container with a 1 mL [redacted] (b) (4) metering pump. [redacted] (b) (4) The target deliverable weight for the configuration (whole bottle) is 112 grams. The target dispensed weight per pump actuation is 1 gram, containing 20 mg of diclofenac sodium. As demonstrated by the characterization data (see the review in 3.2.P.2.4), neither the applied force nor speed impacts the dispensed weight, as long as the minimum force is applied to complete a full actuation, and the [redacted] (b) (4) pump is capable of delivering a consistent amount (1 gram) of drug product per actuation. The safety of the container closure system is supported by the extractables and leachables data. The extractables observed above the analytical evaluation thresholds (AETs) calculated using the safety concern threshold of 1.5 µg/day are [redacted] (b) (4) and [redacted] (b) (4) which are not of safety concern according to Pharm/Tox. The applicant has provided 18 months leachables data for the 25 ºC/60%RH stability condition and 6 months leachables data for the 40 ºC/75%RH stability condition for the three registration stability batches. Although some unknown leachable peaks were found above the analytical evaluation threshold (AET) calculated based on the safety qualification threshold of [redacted] (b) (4) µg/day (the same qualification was recommended by the FDA for the Pennsaid 1.5% product) under the 40 ºC/75%RH stability condition, no leachables were observed above the AET at the 25 ºC/60%RH stability condition for 18 months.

It should be noted that although the to-be-marketed formulation is the same as that evaluated in the clinical program, the container closure system has evolved during development. The clinical supplies for the pivotal safety and efficacy study used the so-called [redacted] (b) (4) container/pump system, which as shown by the controlled lab test data and the data from the clinicians, delivered very variable weights of the solution per actuation. As per this reviewer's communications with Dr. Ellen Fields, the clinical team concluded that 2 pump actuations (2 grams of solution) per knee is the recommended dose despite the [redacted] (b) (4) container/pump system used in the safety/efficacy clinical trial did not accurately deliver 2 gram dose. To this end, the proposed to-be-marketed container/closure [redacted] (b) (4) is fit for purpose as it consistently delivers 1 g of solution per pump actuation.

The drug substance, diclofenac sodium USP, is manufactured by ESTEVE QUIMICA, S.A. in Barcelona, Spain. The drug substance information is provided in the DMF [redacted] (b) (4).

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

The recommended dose is 40 mg diclofenac sodium (two pump actuations) per painful knee, twice daily.

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The proposed expiration dating period is 24 months and the storage statement is "Stored at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]." Considering that no significant changes have been observed based on 6 months stability data for the registration batches [redacted] (b) (4) at both 25 ºC/60% RH and 40 ºC/75% RH, the 18 months leachables data for the registration batches at 25 ºC/60% RH, and the supporting 18 months stability data for the phase 2 safety/efficacy study batch ([redacted] (b) (4) container, not to-be-marketed) at 25 ºC/60% RH, this reviewer concurs with the proposed 24-month expiration dating period.

C. Basis for Approvability or Not-Approval Recommendation

The NDA has provided adequate information to ensure the identity, purity, strength, and quality of the drug product in the proposed multi-dose container with a metering pump.

[redacted] (b) (4)

III. Administrative

A. Reviewer's Signature

See DARRTS.

B. Endorsement Block

See DARRTS.

C. CC Block

See DARRTS.

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Reference ID: 3254049

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

/s/

YONG HU
02/01/2013
Corrected version.

PRASAD PERI
02/01/2013
I concur