CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-348

CHEMISTRY REVIEW(S)

Memorandum

Date: June 10, 2009

From: Martin Haber, Ph.D., Review Chemist

Subject: Chemistry Recommendation and Conclusion on Approvability

To: NDA 22-348 Caldolor (Ibuprofen) Injection

An overall recommendation of Acceptable for manufacturing establishments for this NDA has been received from the Office of Compliance, dated 6/10/09, see attachment.

Since there are no other issues, the chemistry recommendation is changed to Approval.

R/D Init by: Dr. Ali Al-Hakim, Branch Chief, DPAI, BII

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22348/020	Sponsor:	CUMBERLAND PHARMS
Org. Code:	170		2525 WEST END AVE STE 950
Priority:	5F		NASHVILLE TN 37203-1818
Stamp Date:	17-DEC-2008	Brand Name:	CALUDOX INJECTION
PDUFA Date:	17-JUN-2009	Estab. Name:	
Action Goal:		Generic Name:	IBUPROFEN INJECTION
District Goal:	18-APR-2009	Dosage Form:	(INJECTION)
		Strength:	100 MG/ML

FDA Contacts:	K. DAVIES	Project Manager	(HFD-170)	301-796-2205
	M. HABER	Review Chemist		301-796-1675
	A. AL HAKIM	Team Leader		301-796-1323

Overall Recommendation: ACCEPTABLE on 10 JUN 2009 by E. JOHNSON (HFD-320) 301-796-3324

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

DMF No: AADA:

Responsibilities: (b) (4)

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

Last Milestone: (b) (4)

Milestone Date: 18-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-APR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

DMF No: **AADA:**

Responsibilities: (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: **AADA:**

Responsibilities: (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-JAN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

Martin Haber
6/10/2009 01:40:01 PM
CHEMIST

Ali Al-Hakim
6/10/2009 01:48:26 PM
CHEMIST

NDA 22-348

Caldolor (Ibuprofen) Injection

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Cumberland Pharmaceuticals
2525 West End Avenue, Suite 950,
Nashville, TN 37203

Indication: Ibuprofen Injection is indicated for the management of pain and the reduction of fever.

Presentation: The drug product will be available in two strengths, 400 mg (4 mL in a (b) (4) vial) and 800 mg (8 mL in a (b) (4) vial). The vials are made from (b) (4) clear glass and are closed with a (b) (4) stopper and (b) (4) flip-off seal.

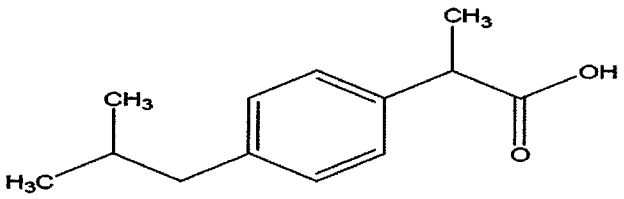
EER Status:	Recommendations:	Pending
Consults:	**EA –**	**Categorical exclusion provided**
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	**Not recommended**
	Biopharm–	N/A
	Microbiology –	**Acceptable**
	Pharm/toxicology –	**Acceptable**

Original Submission: 12-March-2008
Re-submissions: N/A
Post-Approval CMC Agreements: None beyond the typical stability commitments.

Background:
The application is filed as a 505(b)(2), priority NDA based on the approved **NDAs, Children's Motrin® (ibuprofen) ora**l suspension (NDA 20-516), Advil® Liqui-gels (ibuprofen) capsules (NDA 20-402) and Motrin® (ibuprofen) tablets (NDA 17-463). The application was granted priority review status since there is a medical need for injectable antipyretics in patients unable to take oral

medications. Currently, there are no intravenous antipyretic medications approved in the US.

Drug Substance:
The drug substance, **ibuprofen**, is a non-steroidal anti-inflammatory drug (NSAID). It is a well characterized compound that is the subject of EP, JP, and USP monographs. Ibuprofen was first approved by the FDA in 1974. It contains one chiral center but is produced as the racemate.
Chemical structure, chemical name, molecular formula and molecular weight:



(RS)-2-(4-isobutylphenyl) propionic acid; (±)-p-Isobutylhydratropic acid;
(±)-2-(p-Isobutylphenyl) propionic acid
Molecular formula: C13H18O2
Molecular weight: 206.28

The drug substance is produced by [redacted] (b) (4). Most of the CMC information for the drug substance is referred to DMF (b) (4) [redacted] which has been reviewed and found acceptable.
USP tests for the drug substance include identification, water content, assay, purity (HPLC), heavy metals, residue on ignition, and organic volatile impurities.
The drug product manufacturer tests the incoming drug substance for identification, microbial count and bacterial endotoxin tests to ensure its appropriateness for use as an injectable drug product.
Conclusion: The drug substance is satisfactory.

Drug Product:
The drug product, Caldolor (Ibuprofen) Injection, is a clear sterile aqueous solution for injection containing 100 mg/mL of ibuprofen with 78 mg/mL of arginine (b) (4) [redacted]. **It is available in** two strengths; 400 mg (4 mL in a [redacted] (b) vial) and 800 mg (8 mL in a [redacted] (b) (4) vial). The vials are (b) (4) [redacted] clear glass and are closed with a (b) (4) [redacted] stopper and (b) (4) [redacted] flip-off seal. Ibuprofen Injection is intended to be added to commercially available 250 mL bags of 0.9% Sodium Chloride (normal saline, NS), 5% Dextrose (D5W) or Lactated Ringers Solution (LRS) prior to clinical use and infused over a 10 to 30 minute period. Testing demonstrated that the drug

product was compatible with NS, D5W and LRS for at least 24 hours at room temperature.

The drug product formulation uses the amino acid (b) (4) rginine, USP (b) (4) . A (b) (4) ibuprofen.

Arginine is present in the product at a molar ratio of 0.92:1 arginine:ibuprofen.

The pH is adjusted with (b) (4) l to pH 7.4. There are (b) (4) in the drug product formulation. (b) (4)

The drug product is manufactured b (b) (4) (b) (4). (b) (4)

The drug product vials are then (b) (4)

In-process controls include tests for pH, fill volume, (b) (4) sterilization cycle conditions and visual inspection. Drug product specifications include (b) (4) as per ICH Q3B in response to a request from the Agency.

The submitted stability test data for 48 months of drug product stored at 25°C demonstrated adequate drug product stability and support 48 months of expiry dating.

Conclusion: The drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending acceptable overall cGMP recommendation from the Office of Compliance.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

Container labels

(b) (4)

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/s/

Ali Al-Hakim
5/27/2009 01:39:51 PM
CHEMIST

NDA 22-348

Caldolor (Ibuprofen) Injection

Cumberland Pharmaceuticals

Martin Haber, Ph.D.
Division of Pre-Marketing Assessment I

For
Division of Anesthesia, Analgesia and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 22-348

2. REVIEW #1

3. REVIEW DATE: May 20, 2009

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 22-348 74-day letter	2/24/09
NDA 22-348 CMC IR letter	4/7/09

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12/3/08
Amendment	3/11/09
Amendment	4/20/09
Amendment	5/12/09

7. NAME & ADDRESS OF APPLICANT:

Name:	Cumberland Pharmaceuticals
Address:	2525 West End Avenue, Suite 950, Nashville, TN 37203
Representative:	Amy Rock, Ph.D., Senior Manager, Regulatory Affairs
Telephone:	615-255-0068

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Caldolor
b) Non-Proprietary Name (USAN): Ibuprofen
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (new formulation and dosage form)
- Submission Priority: Priority

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

10. PHARMACOL. CATEGORY: Non-steroidal anti-inflammatory drug (NSAID, COX 1 and COX 2 inhibitor) indicated for management of pain and for reduction of body temperature in fever

11. DOSAGE FORM: Sterile aqueous solution for intravenous injection

12. STRENGTH/POTENCY: 400 and 800 mg vials, 100 mg/mL concentration

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

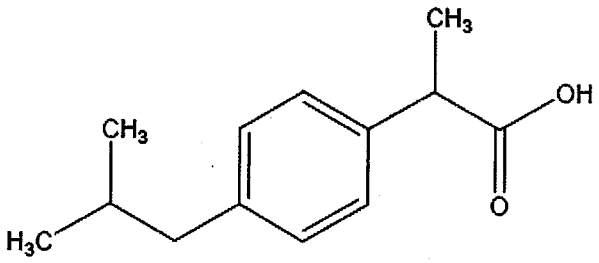
__X___Not a SPOTS product

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

Compendial Name: **Ibuprofen**

CAS Number: 15687-27-1

Chemical Names: (RS)-2-(4-isobutylphenyl) propionic acid; (±)-*p*-Isobutylhydratropic acid; (±)-2-(*p*-Isobutylphenyl) propionic acid



Molecular formula: $C_{13}H_{18}O_2$

Relative Molecular Mass: 206.28

Stereochemistry: Racemic mixture

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4) (b) (4)	Ibuprofen	3	Adequate	6/2/08	Reviewed by Dr. Y. Amin
	III	(b) (4) (b) (4)	(b) (4) (b) (4) (b)	4	Adequate		
	III	(b) (4) (b)	(b)(b) (4) (b) (4) (b) (4)	4	Adequate		
	III	(b) (4) (b) (4) (b) (4)	(b) (4)	4	Adequate		

[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
	NDA 20-516	**Children's Motrin (suspension, oral)**
	NDA 20-402	Advil Liqui-Gels (capsule, oral)
	NDA 17-463	Motrin (tablet, oral)
	IND 62,605	Ibuprofen IV clinical studies

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharmacology/Toxicology	Approval	5/13/09	Dr. A. Mukherjee
Methods Validation	Not required		
OSE/Labeling/Tradename	Acceptable with revisions		
EA	Acceptable, Categorical Exclusion	3/30/09	M. Haber
Microbiology	Approval	5/6/09	Dr. V. Pawar

The Chemistry Review for NDA 22-348

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval, pending a satisfactory cGMP inspection report (EER)

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

Not Applicable

II. Summary of Chemistry Assessments

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

The drug product, Caldolor (Ibuprofen) Injection, is a clear sterile aqueous solution for injection containing 100 mg/mL of ibuprofen with 78 mg/mL of arginine(b) (4) [redacted]. It is available in two strengths, 400 mg (4 mL in a (b) (4) vial) and 800 mg (8 mL in a (b) (4) vial). The (b) (4) clear glass vials are closed with a (b) (4) [redacted] stopper and (b) (4) [redacted] flip-off seal. Ibuprofen Injection is indicated for the management of pain and the reduction of fever.

The drug product formulation uses the amino acid (b) Arginine, USP as an (b) (4) [redacted] At (b) (4) [redacted] ibuprofen. Arginine is present in the product at a molar ratio of 0.92:1 arginine:ibuprofen. The pH is adjusted with (b) (4) [redacted] to pH 7.4. There are (b) (4) [redacted]. (b) (4) [redacted] The drug product is manufactured at (b) (4) [redacted] had an acceptable cGMP status as of 4/30/09. EES for the drug product manufacturer in (b) (4) [redacted] is pending.

The drug product is manufactured using (b) (4) [redacted] for sterile injectable solutions. (b) (4) [redacted] The (b) (4) [redacted]. The filling process uses (b) (4) [redacted] (b) (4) [redacted] The drug product vials are then (b) (4) [redacted] The product quality microbiology review for sterility assurance dated 5/6/09 by Dr. V. Pawar recommends NDA approval.

In-process controls include tests for pH, fill volume, (b) (4) sterilization cycle conditions and inspection. Drug product specifications include (b) (4) as per ICH Q3B in response to a request from the Agency. In the 4/20/09 Amendment, the volume in container specification added the 8 mL volume. Methods are adequate and validated.

The container/closure system is typical for an injectable product and involves (b) (4) clear glass vials: two (b) vials, one with a (b) mm diameter neck and the other with a (b) mm diameter neck, and one (b) (4) mm diameter neck vial. The vials are closed with either a (b) (4) mm diameter (b) (4) stopper. There is also an (b) (4) flip-off seal cover. A reflux extraction study with the drug formulation found no extractables released from the stopper components.

The drug substance, **ibuprofen**, is a non-steroidal anti-inflammatory drug (NSAID). It is a well characterized compound that is the subject of EP, JP, and USP monographs. Ibuprofen was first approved by the FDA in 1974. It contains one chiral center but is produced as the racemate. It is a carboxylic acid with a molecular weight of 206.28. Ibuprofen is manufactured and tested at (b) (4), as it has been for the last (b) years. (b) (4) is the holder of DMF (b) (4) for Ibuprofen. The site was last found to have acceptable cGMP status on 12/18/08.

Most specific CMC information for the drug substance is referred to DMF (b) (4) which has been reviewed 11 times by the Agency. The most recent review dated 6/2/08 found the DMF adequate and there has been no revision to the DMF since the last review. The drug substance is produced by (b) (4) Further review of drug substance manufacturing was not required for this NDA. The drug product manufacturer tests the drug substance for identification, microbial count and bacterial endotoxin to ensure its appropriateness for use in an injectable product.

In the 4/7/09 IR letter, the NDA sponsor was asked to tighten the limits for (b) (4) impurities in the drug substance specifications since the drug product is intended for intravenous injection into very sick patients unable to take oral medications and the maximum daily dose is greater than 2 grams. In the 4/20/09 Amendment, the sponsor agreed to tighten the specification acceptance

limits for known impurities to NMT (b)% and to NMT (b)% for unknown impurities. The sponsor also agreed to report all batch analysis data to two decimal places and identify impurities by name or relative retention time.

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

Ibuprofen Injection vials are for single use only and do not contain any preservative. Dosage for adults is 400 or 800 mg every 6 hours as necessary for relief of pain or fever. In order to avoid any potential for local irritation due to administering undiluted drug, Ibuprofen Injection is intended to be added to commercially available 250 mL bags of 0.9% Sodium Chloride (normal saline, NS), 5% Dextrose (D5W) or Lactated Ringers Solution (LRS) prior to clinical use and infused over a 10 to 30 minute period. Testing demonstrated that the drug product was compatible with NS, D5W and LRS for at least 24 hours at room temperature. The drug product is stored at controlled room temperature 20° to 25°C with an expiry of(b) (4)). Submitted data for 48 months of drug product storage at 25°C demonstrated adequate drug product stability.

C. Basis for Approvability or Not-Approval Recommendation

The firm has adequately responded (3/11/09 and 4/20/09 Amendments) to all chemistry deficiencies. There are no pending chemistry issues other than EES.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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/s/

Martin Haber
5/21/2009 05:42:11 PM
CHEMIST

Ali Al-Hakim
5/22/2009 01:32:33 PM
CHEMIST