CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-565

CHEMISTRY REVIEW(S)

NDA 22-565

Advil® Cold & Sinus PE Caplets
Ibuprofen 200 mg/Phenylephrine HCl 10 mg Caplets (OTC)

Wyeth Consumer Healthcare

Gene W. Holbert, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

CMC REVIEW OF NDA 22-565
For the Division of Division of Nonprescription Clinical Evaluation

Table of Contents

CMC Review Data Sheet

1. NDA 22-565

2. REVIEW #: 1

3. REVIEW DATE: 10-DEC-2009

4. REVIEWER: Gene W. Holbert, Ph.D.

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	July 28, 2009
Amendment	August 13, 2009
Amendment	September 3, 2009
Amendment	September 18, 2009
Amendment	October 23, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth Consumer Healthcare
Address:	5 Giralda Farms Madison, NJ 07940
Representative:	Erica Sinclair, Senior Manager Global Regulatory Affairs
Telephone:	(973) 660-6341

8. DRUG PRODUCT NAME/CODE/TYPE:

   a. Proprietary Name: Advil® Cold & Sinus PE
   b. Non-Proprietary Name: Ibuprofen 200 mg/Phenylephrine HCl 10 mg Caplets
   c. Code Name/#:
   d. Chem. Type/Submission Priority:
      - Chem. Type: 4
      - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-inflammatory, analgesic, antipyretic/nasal decongestant

CMC Review Data Sheet

11. DOSAGE FORM: Tablet, film-coated CODE: 504

12. STRENGTH/POTENCY: Ibuprofen, 200 mg; phenylephrine HCl, 10 mg

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

14. Rx/OTC DISPENSED: ___Rx ___√___OTC

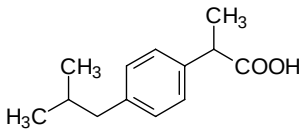
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___√___Not a SPOTS product

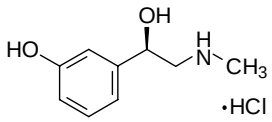
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN/INN: Ibuprofen
CAS: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-



Molecular Formula: $C_{13}H_{18}O_2$ Molecular Weight: 206.28 CAS: 58560-75-1 (±)

USAN/INN: Phenylephrine hydrochloride
CAS: (α*R*)-3-Hydroxy-α-[(methylamino)methyl]benzenemethanol hydrochloride



Molecular Formula: $C_9H_{13}NO_2 \cdot HCl$ Molecular Weight: 203.67 CAS: 61-76-7

17.RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Ibuprofen	3	Adequate	24-AUG-2006 R.E. Powers	LOA Dec. 3, 2008
	II	(b) (4)	Phenylephrine HCl	1	Adequate	07-DEC-2007 G Holbert	LOA Oct. 22, 2009
	III	(b) (4)		3	Adequate	16-JAN-2005 C. Bertha	LOA Jan. 20, 2009
	III			3	Adequate	22-MAY-2002 L. Roca	LOA Jan. 14, 2009
	III			3	Adequate	16-JUL-2004 A. Agarwal	LOA Dec. 3, 2008

[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: None

CMC Review Data Sheet

18.STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	05-OCT-2009	M. Stock
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to current ONDQA policy		
DMETS	N/A		
EA	Categorical exclusion granted under the provisions of 21 CFR 25.31 (a)	02-DEC-2009	G. Holbert
Microbiology	N/A		

The CMC Review for NDA 22-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This resubmission refers to NDA 22-112 for CMC information. NDA 22-112 was previously found to contain sufficient information to assure identity, strength, purity and quality. Labeling is acceptable. The Office of Compliance has issued an overall "Acceptable" recommendation.

Therefore, this application is recommended for approval from the CMC perspective.

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

None.

II. Summary of CMC Assessments

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

Advil® Cold and Sinus PE Caplets are tan, film-coated oval shaped tablets printed on one side with "Advil C&S PE" in black ink. Each tablet contains 200 mg of Ibuprofen USP and 10 mg Phenylephrine Hydrochloride USP. Inactive ingredients include Acesulfame Potassium, Carnauba Wax, Colloidal Silicon Dioxide, Croscarmellose Sodium, Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Propyl Gallate, Pregelatinized Starch, Sodium Lauryl Sulfate, Corn Starch, Stearic Acid, Sucralose and (b) (4) With the exception of the flavoring, film coating, and printing ink, all excipients are compendial. The flavoring, film coating and ink are composed of ingredients that are compendial and/or GRAS.

DMEPA has found the proprietary name Advil® Cold and Sinus PE unacceptable at this writing since the term "PE" has apparently been used for both phenylephrine- and pseudoephedrine-containing products.

The product is packaged in (b) (4) white, opaque blisters with child-resistant lidding. Each blister card contains ten tablets which are packaged in cardboard cartons. Each carton contains (b) (4), 20 (b) (4) tablets. A one-count pouch constructed from white (b) (4) will also be available.

Advil™ Cold and Sinus PE Caplets are manufactured by Wyeth Consumer Healthcare, Guayama, PR. The manufacturing process consists of (b) (4)

(b) (4)

All Module 3 (Quality) information is cross referenced to NDA 22-112.

The drug product specification includes tests for Appearance, Ibuprofen Identity and Assay, Phenylephrine Identity and Assay, Uniformity of Dosage Units for each active ingredient, Assay for Specified Degradants for each active ingredient, Unspecified Degradants related to each active ingredient, Total Degradants/Unspecified Peaks, and Dissolution. As amended, NDA 22-112 contained 12 months of long term stability data on three full scale registration batches manufactured by Wyeth Consumer Healthcare. There were no significant changes in any of the lots stored at the long term, intermediate or accelerated condition. The applicant has proposed an 18 month expiration date when stored at 20-25ºC (68-77ºF) and protected from freezing.

Since this is an OTC product, there is no package insert. The NDA 22-112 labeling was reviewed by the Division of Over-the-Counter Drug Products and found acceptable.

The active drug substances are ibuprofen and phenylephrine hydrochloride. Ibuprofen, a white to almost white powder or crystals with a characteristic odor, is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and anti-pyretic properties. Ibuprofen is approved in over 100 countries worldwide and has been marketed in the US for over 20 years as an ingredient in over-the-counter drug products. Ibuprofen is supplied as a racemic mixture (b) (4) Ibuprofen is described in (b) (4) DMF (b) (4).

Phenylephrine hydrochloride is a white or almost white powder or crystals primarily used as a nasal decongestant. It has been available in over-the-counter drug products since the early 1960s. (b) (4) supplies the drug substance. Phenylephrine hydrochloride is described in (b) (4) DMF (b) (4).

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

Advil™ Cold and Sinus PE is indicated for relief of headache, sinus pressure, nasal congestion, fever and minor aches and pains. Adults and children 12 years and over: should take 1 caplet every 4 hours while symptoms persist. Not more than 6 caplets in any 24-hour period should be taken unless directed by a physician. For children less than 12 years of age, a physician should be consulted.

C. Basis for Approvability or Not-Approval Recommendation

The referenced NDA 22-112 has adequate controls for raw materials. Manufacturing processes are robust and adequately controlled. Specifications are adequate to ensure the identity, strength, quality, and purity of the drug product. The container/closure system is adequate to protect the drug product. The product will be stable over the proposed

expiration dating period (18 months) when stored as labeled. Labeling is acceptable. All facilities inspections are in compliance with cGMP.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

B. Endorsement Block:

Gene W. Holbert, Ph.D.
Moo-Jhong Rhee, Ph.D., Branch Chief, Branch III, ONDQA

C. CC Block: *entered electronically in DARRTS*

8 Pages has been withheld immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22565	ORIG-1	WYETH CONSUMER HEALTHCARE	ADVIL COLD & SINUS PE(IBUPROFEN 200MG/PH

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

/s/

GENE W HOLBERT
01/04/2010

MOO JHONG RHEE
01/04/2010
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	22-565
Applicant:	Wyeth Consumer Healthcare
Stamp Date:	July 28, 2009
PDUFA Date:	Jan. 28, 2010
Trademark:	Advil® Cold & Sinus PE
Established Name:	Ibuprofen and phenylephrine HCl
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Temporary relief of symptoms associated with the common cold or flu.
PAL:	Shulin Ding, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

NDA 22-565 is the resubmission of NDA 22-112 Advil Cold & Sinus PE (ibuprofen 200 mg/phenylephrine HCl 10 mg) caplets. NDA 22-112 received a "not approvable" action from its first cycle review due to ClinPharm issues. The CMC section of NDA 22-112 was deemed adequate at the end of the first cycle review. CMC review #1and its addendum stated that there were no outstanding CMC deficiencies, and recommended that the NDA be approved per CMC perspective.

The resubmission is assigned with a new NDA number because NDA 22-112 is a 505(b)(2) submission and there are some changes in the information regarding referenced drug(s) in the resubmission when compared with NDA 22-112 original submission. According to Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), the applicant is not allowed to make changes in the referenced drug for a 505(b)(2) NDA but can elect to withdraw the original NDA and submit a new 505(b)(2) NDA.

No information is provided under Module 3 (Quality section) of NDA 22-565. The applicant in the cover letter references NDA 22-112 for information. Carton/container labels and labeling are provided in Module 1 of the original submission of NDA 22-565, Environmental Analysis is in the 8/13/09 amendment, proprietary name is in the 8/27/09 amendment, and establishment information is in the 9/18/09 amendment.

B. Critical issues for review

- The applicant does not clearly state that there are no changes in CMC for this resubmission. A clarification needs to be sought.

- Updated Letters of Authorization need to be provided for all referenced DMFs.

C. Comments for 74-Day Letter

Request the applicant to provide the following information to facilitate the review:

- Clarify if there is any CMC information which is different from that in NDA 22-112.

- Provide updated Letters of Authorization for all referenced DMFs.

D. Recommendation**:**

This NDA is fileable from the CMC perspective.

Manufacturing/testing facilities are located in (b) (4) GMP inspection requests have been submitted.

Shulin Ding
Pharmaceutical Assessment Lead

Moo-Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists;

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists;

1. Drug Substances: Referenced to NDA 22-112 and DMFs (b) (4)

		Does the section contain synthetic scheme with in-process parameters?	Not applicable
		Does the section contain structural elucidation data?	Not applicable
		Does the section contain specifications?	Not applicable
		Does the section contain information on impurities?	Not applicable
		Does the section contain validation data for analytical methods?	Not applicable
		Does the section contain container and closure information?	Not applicable
		Does the section contain stability data?	Not applicable

2. Drug Product: Referenced to NDA 22-112

		Does the section contain manufacturing process with in-process controls?	Not applicable
		Does the section contain quality controls of excipients?	Not applicable
		Does the section contain information on composition?	Not applicable
		Does the section contain specifications?	Not applicable
		Does the section contain information on degradation products?	Not applicable
		Does the section contain validation data for analytical methods?	Not applicable
		Does the section contain information on container and closure systems?	Not applicable
		Does the section contain stability data with a proposed expiration date?	Not applicable
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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

/s/

SHULIN DING
09/24/2009

MOO JHONG RHEE
09/24/2009
Chief, Branch III