

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022113Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-113

Advil Allergy & Congestion Relief

Pfizer Consumer Healthcare

Swapam K De, Ph.D.

CMC-Lead

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment III

Branch VII

CMC REVIEW OF NDA 22-113

**For the Division of Nonprescription Clinical Evaluation
(HFD-560)**

Chemistry Assessment Section

Introduction:

The proposed drug product contains three drug substances: Ibuprofen, Phenylephrine HCl, and Chlorpheniramine Maleate. Advil® Allergy & Congestion Relief are gray film-coated oval shaped tablets. Each tablet contains 200 mg Ibuprofen USP, 10 mg Phenylephrine Hydrochloride USP, and 4 mg Chlorpheniramine Maleate. Chemistry review #1 contains details of the Chemistry, Manufacturing and Controls information for the drug substances and drug product.

Background:

The second review cycle of NDA 22-113 is a response to Agency letter dated July 25, 2008. The original application was submitted by Wyeth Consumer Healthcare on September 25, 2008. Chemistry review #1 (see review by Bogdan Kurtyka dated June 11, 2008) has no outstanding issues from a CMC perspective and was recommended for “Approval” pending satisfactory completion of cGMP inspections. The complete response letter issued on July 25, 2008 included following deficiency on inspection issue.

“One of the facilities involved in your submission is deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility is required to assure identity, strength, purity and quality of the drug product.”

The pending EER issue for the chemistry, manufacturing and controls for the NDA 22-113 (Advil® Allergy & Congestion Relief) is resolved on December 4, 2011 and it is acceptable (see attached EER summary report).



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application: NDA 22113/000 **Action Goal:**
Stamp Date: 25-SEP-2007 **District Goal:** 22-OCT-2011
Regulatory: 21-DEC-2011
Applicant: PFIZER CONS HLTHCARE **Brand Name:** Advil Allergy & Congestion Relief
 5 GIRALDA FARMS **Estab. Name:**
 MADISON, NJ 07974 **Generic Name:** IBUPROFEN/PHENYLEPHRINR/CHLORPHENI
 RAMINE
Priority: 4S **Product Number; Dosage Form; Ingredient; Strengths**
Org. Code: 560 001; TABLET; IBUPROFEN; 200MG
 001; TABLET; PHENYLEPHRINE HYDROCHLORIDE; 10MG
 001; TABLET; CHLORPHENIRAMINE MALEATE; 4MG
Application Comment: NDA RESUBMISSION ON JUN 21, 2011. (on 02-AUG-2011 by Y. LIU ())
FDA Contacts: Y. LIU Project Manager
 S. DE Review Chemist 301-796-1664
 S. DE Team Leader 301-796-1664

Overall Recommendation:	ACCEPTABLE	on 04-DEC-2011	by M. STOCK	(HFD-320)	301-796-4753
	PENDING	on 02-AUG-2011	by EES_PROD		
	PENDING	on 02-AUG-2011	by EES_PROD		
	PENDING	on 02-AUG-2011	by EES_PROD		
	PENDING	on 02-AUG-2011	by EES_PROD		
	WITHHOLD	on 24-JUL-2008	by C. CRUZ	(HFD-323)	301-796-3254

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: (b) (4)
DMF No:
Responsibilities:
Establishment Comment:
Profile:

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-APR-2008				KURTYKAB
OC RECOMMENDATION	21-APR-2008			ACCEPTABLE BASED ON PROFILE	KIEL
SUBMITTED TO OC	02-AUG-2011				LIUY
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment:

(b) (4)

DMF No:

Responsibilities:

Establishment

Comment:

Profile:

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-APR-2008				KURTYKAB
SUBMITTED TO DO	22-APR-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	27-MAY-2008	GMP Inspection			ADAMSS
OC RECOMMENDATION	24-JUL-2008 (b) (4)			WITHHOLD	CRUZC
THE LATEST SITE INSPECTION (b) (4) WAS INITIALLY OAI AND RECLASSIFIED AS VAI BASED ON THE FIRM'S RESPONSE. INSPECTION IS NECESSARY BEFORE APPLICATION RECOMMENDATION.				BASED ON FILE REVIEW	
INSPECTION PERFORMED	25-SEP-2008		25-SEP-2008		BRUCE.MCCULLOUGH
<p>This was a PAI & CGMP EI of an API mfg site, initiated by CDER/DFI (FACTS assn (b) (4) covering the mfg of the 2 API's currently being shipped to U.S.: phenylephrine HCl (b) (4) and pilocarpine HCl (b) (4). Coverage included the repeat process validation study for pilocarpine HCl, after process validation deficiencies cited in the last FDA EI. Coverage included qualification of a new production line for phenylephrine HCl, as described in DMF (b) (4) supplement dated 3/23/07. DMF (b) (4) is referenced in NDA 21-113, Ibuprofen/Phenylephrine HCl/Chlorpheniramine Maleate Tablets (Applicant: Wyeth Company, Madison, NJ). The EI covered 5 CGMP systems: Quality, Facilities and Equipment, Materials, Production, and Laboratory Controls. Operations are limited to 1 profile class: CSN. Coverage was made per C.P.'s 7356.002F & 7346.832.</p> <p>The last EI (b) (4) was a CGMP and pre-approval EI, covering ANDA 76-746, Pilocarpine HCl Tablets (classified VAI), which found CGMP deviations relating to pilocarpine HCl manufacture, including: inadequate cleaning of non-dedicated equipment; unvalidated test methods used in cleaning validation; process validation deficiencies; and stability testing deficiencies. A 7-point FDA-483 was issued.</p> <p>At start of current EI, I presented credentials to (b) (6) General Managing Director, (b) (4) Plant Manager (the most responsible person at the site). The current EI revealed 1 CGMP deviation: failure to add at least one batch of Phenylephrine HCl per year to the stability testing program. A 1-item FDA-483 was issued to (b) (6) who promised corrective action.</p> <p>6 other items were discussed with mgmt:</p> <ul style="list-style-type: none"> - The SOP for handling OOS test results directs that, when there is no conclusive evidence of lab error, (b) (4) retests are to be performed and, if (b) (4) retest results are within specification, the average of (b) (4) retests is taken as representing the batch, and t 					
OC RECOMMENDATION	21-MAY-2010	APPEARS THIS WAY ON ORIGINAL		WITHHOLD	STOCKM
				ADMIN CLOSURE-IGNORE RECCOMEND	
SUBMITTED TO OC	02-AUG-2011				LIUY
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Chemistry Assessment Section

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment:

(b) (4)

DMF No:

Responsibilities:

Establishment
Comment:
Profile:

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-APR-2008				KURTYKAB
OC RECOMMENDATION	22-APR-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	02-AUG-2011				LIUY
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: FEI: 3007343300

PFIZER CONSUMER HEALTHCARE

CARR # 3 KM 142.1
GUAYAMA, PR 00784

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment
Comment:

Profile: TABLETS, PROMPT RELEASE

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2011				LIUY
SUBMITTED TO DO	16-AUG-2011	10-Day Letter			TOULOUSEM
DO RECOMMENDATION	01-DEC-2011			ACCEPTABLE	RHERNAND
ACCEPTABLE RECOMMENDATION BASED ON FILE REVIEW. LAST ESTABLISHMENT INSPECTION PERFORMED ON (b) (4) AND PROFILES PLACED ACCEPTABLE (TCM) ON 11/30/2011				BASED ON FILE REVIEW	
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: 1119620 FEI: 1119620
 PFIZER, INC. CONSUMER HEALTHCARE
 1211 SHERWOOD AVE
 RICHMOND, VA 232201212

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-APR-2008				KURTYKAB
SUBMITTED TO DO	28-APR-2008	GMP Inspection			FERGUSONS
ASSIGNED INSPECTION TO IB	30-APR-2008	Product Specific			BSEEMAN
INSPECTION SCHEDULED	16-JUN-2008		30-JUN-2008		BSEEMAN
INSPECTION PERFORMED	20-JUN-2008		20-JUN-2008		BSEEMAN

THIS CENTER DIRECTED PRE-APPROVAL INSPECTION WAS CONDUCTED IN ACCORDANCE WITH CP 7346.832 AND CP 7356.002 TO COVER NDA 22-113, IBUPROFEN/PHENYLEPHRINE/CHLORPHENIRAMINE MALEATE 200MG/10MG/4MG. THE SITE IS RESPONSIBLE FOR METHOD VALIDATION ACTIVITIES AND FOR STABILITY TESTING OPERATIONS RELATED TO THE SUBMISSION BATCHES OF THE AFOREMENTIONED APPLICATION. THE PROFILE COVERED WAS CTL, CONTROL TESTING LABORATORY. THE LABORATORY SYSTEM WAS COVERED DURING THE CURRENT INSPECTION.

THE LAST INSPECTION OF THE FIRM WAS CONDUCTED ON (b) (4) AND WAS CLASSIFIED NAL. THE INSPECTION WAS LIMITED AND COVERED AN OVERVIEW OF GENERAL OPERATIONS.

CURRENT INSPECTION REVEALED THE FIRM TO CONTINUE OPERATIONS AS A CONTROL TESTING LABORATORY FOR WYETH PRODUCTS ONLY. NO FDA-483 WAS ISSUED AT THE CLOSE OF THE INSPECTION; HOWEVER, SEVERAL DISCUSSION ITEMS WERE BROUGHT TO THE FIRM'S ATTENTION INCLUDING: SAMPLE ACCOUNTABILITY AND TRAINING AND TIMELINESS OF LITERATURE REVIEWS IN REGARDS TO RESEARCH AND DEVELOPMENT OPERATIONS RELATING TO DEGRADATION PRODUCTS. THE FIRM ACKNOWLEDGED THE DISCUSSION ITEMS. A RECOMMENDATION FOR THE APPROVAL OF THE SITE IN REGARDS TO THE AFOREMENTIONED APPLICATION WILL BE SUBMITTED TO CDER.

NO SAMPLES WERE COLLECTED AND NO REFUSALS WERE ENCOUNTERED.

INSPECTION PERFORMED	20-JUN-2008		20-JUN-2008		BROOKE.HIGGINS
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See Turbo EIR.

Post-inspectional correspondence should be sent to:
 Larry E. Small, Ph.D., Sr. VP Global Product Development
 PO Box 26609
 Richmond, VA 23261

DO RECOMMENDATION	01-JUL-2008			ACCEPTABLE INSPECTION	BSEEMAN
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THIS CENTER DIRECTED PRE-APPROVAL INSPECTION WAS CONDUCTED IN ACCORDANCE WITH CP 7346.832 AND CP 7356.002 TO COVER NDA 22-113, IBUPROFEN/PHENYLEPHRINE/CHLORPHENIRAMINE MALEATE 200MG/10MG/4MG. THE SITE IS RESPONSIBLE FOR METHOD VALIDATION ACTIVITIES AND FOR STABILITY TESTING OPERATIONS RELATED TO THE SUBMISSION BATCHES OF THE AFOREMENTIONED APPLICATION. THE PROFILE COVERED WAS CTL, CONTROL TESTING LABORATORY. THE LABORATORY SYSTEM WAS COVERED DURING THE CURRENT INSPECTION.

THE LAST INSPECTION OF THE FIRM WAS CONDUCTED ON (b) (4) AND WAS CLASSIFIED NAL. THE INSPECTION WAS LIMITED AND COVERED AN OVERVIEW OF GENERAL



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

OPERATIONS.

CURRENT INSPECTION REVEALED THE FIRM TO CONTINUE OPERATIONS AS A CONTROL TESTING LABORATORY FOR WYETH PRODUCTS ONLY. NO FDA-483 WAS ISSUED AT THE CLOSE OF THE INSPECTION; HOWEVER, SEVERAL DISCUSSION ITEMS WERE BROUGHT TO THE FIRM'S ATTENTION INCLUDING: SAMPLE ACCOUNTABILITY AND TRAINING AND TIMELINESS OF LITERATURE REVIEWS IN REGARDS TO RESEARCH AND DEVELOPMENT OPERATIONS RELATING TO DEGRADATION PRODUCTS. THE FIRM ACKNOWLEDGED THE DISCUSSION ITEMS. A RECOMMENDATION FOR THE APPROVAL OF THE SITE IN REGARDS TO THE AFOREMENTIONED APPLICATION WILL BE SUBMITTED TO CDER.

NO SAMPLES WERE COLLECTED AND NO REFUSALS WERE ENCOUNTERED.

OC RECOMMENDATION	01-JUL-2008	ACCEPTABLE	FERGUSONS
		DISTRICT RECOMMENDATION	
SUBMITTED TO OC	02-AUG-2011		LIUY
OC RECOMMENDATION	04-AUG-2011	ACCEPTABLE	STOCKM
		BASED ON PROFILE	



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: 1120199 FEI: 1120199
 RICHMOND DIVISION OF WYETH
 2248-2300 DARBYTOWN RD
 RICHMOND, VA 232315404

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER

Establishment Comment: THE AMMENDMENT STATES READY FOR INSPECTION AFTER (b) (4)
 MAY USE IBUPROFEN REFERENCE STANDARD PAST THE EXPIRATION DATE
 RELEASE TESTING CONSISTS OF VISUAL IDENTIFICATION TEST. (b) (4) by B. KURTYKA () 301-796-1431

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					<u>Reason</u>
SUBMITTED TO OC	18-APR-2008				KURTYKAB
OC RECOMMENDATION	21-APR-2008			ACCEPTABLE BASED ON PROFILE	KIEL
SUBMITTED TO OC	02-AUG-2011				LIUY
SUBMITTED TO DO	04-AUG-2011	10-Day Letter			STOCKM
DO RECOMMENDATION	05-AUG-2011			ACCEPTABLE BASED ON FILE REVIEW	BSEEMAN
OC RECOMMENDATION	10-AUG-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

Recommendations: From chemistry, manufacturing and controls point of view, this NDA may be approved.

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/s/

SWAPAN K DE
12/05/2011

ALI H AL HAKIM
12/05/2011
I concur

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 25-JUL-2008
To: NDA 22-113 CMC Review #1
From: Bogdan Kurtyka, Ph.D.
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch III ONDQA Division II
CC: Shulin Ding, Ph.D.
Subject: **CMC Recommendation for NDA 22-113 due to recent notification of unacceptable cGMP compliance**

The PDUFA date of NDA 22-113 is 25-JUL-2008. CMC Review #1 was completed on 01-JUN-2008 with a recommendation of Approval action pending an “Acceptable” overall compliance recommendation.

The Office of Compliance has issued an overall rating of “**Withhold**” on 24-JUN-2008. The report is attached below.

Therefore, from a CMC perspective, this NDA is recommended for “Approvable” until the facilities involved are fully in compliance with cGMP requirements to assure identity, strength, purity, and quality of the drug product.

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22113/000 Sponsor: WYETH CONS
Org Code : 560 NO CITY, , XX
Priority : S
Stamp Date : 25-SEP-2007 Brand Name (b) (4)
PDUFA Date : 25-JUL-2008 Estab. Name:
Generic Name:
IBUPROFEN/PHENYLEPHRINR/CHLORPHENIRAMINE
Action Goal : District Goal: 26-MAY-2008
Dosage Form: (TABLET)
Strength : 200MG/10MG/4MG
FDA Contacts: B. KURTYKA Review Chemist 301-796-1431
S. DING Team Leader 301-796-1349

Overall Recommendation: WITHHOLD on 24-JUL-2008 by C. CRUZ (HFD-323) 301-796-3254

Establishment :

DMF No: (b) (4)
Responsibilities:

Profile :
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-APR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMF No: (b) (4)
Responsibilities:

Profile :
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JUL-08
Decision : WITHHOLD
Reason : BASED ON FILE REVIEW

Establishment :

DMF No: (b) (4)
Responsibilities:

Profile :

Last Milestone: OC RECOMMENDATION
Milestone Date: 22-APR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1120199 FEI : 1120199
RICHMOND DIVISION OF WYETH
2248-2300 DARBYTOWN RD
RICHMOND, VA 232315404

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 21-APR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1119620 FEI : 1119620
WYETH CONSUMER HEALTHCARE - PRODUCT DEVELOPMENT
1211 SHERWOOD AVE
RICHMOND, VA 232201212

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 01-JUL-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2650135 FEI : 3003108339
WYETH PHARMACEUTICALS COMPANY
STATE ROAD #3, KM. 142.1
GUAYAMA, PR 00784

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 21-APR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

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

/s/

Bogdan Kurtyka
7/25/2008 10:28:31 AM
CHEMIST

Moo-Jhong Rhee
7/25/2008 10:36:47 AM
CHEMIST
Chief, Branch III

NDA 22-113

(b) (4)

Wyeth Consumer Healthcare

Bogdan Kurtyka, Ph.D.

Review Chemist

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

**CMC REVIEW OF NDA 22-113
For the Division of Nonprescription Clinical Evaluation (HFD-560)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-113
2. REVIEW #: 1
3. REVIEW DATE: 06-01-2008
4. REVIEWER: Bogdan Kurtyka, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	25-Sep-2007
Amendment #0002	18-Dec-2007
Amendment #0006	05-Mar-2008
Amendment #0009	18-Apr-2007
Amendment #0010	16-May-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Consumer Healthcare
Address: 5 Giralda Farms
Madison, NJ 07940
Representative: Neil Napolitano
Telephone: (973)660-5725

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name: Ibuprofen/Phenylephrine HCl/Chlorpheniramine Maleate
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 4
 - Submission Priority: S

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

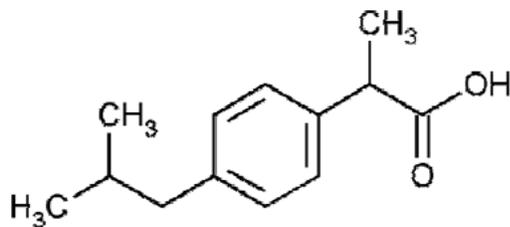
10. PHARMACOL. CATEGORY: Anti-inflammatory analgesic/antipyretic,
ophthalmic vasoconstrictor, antihistamine

CMC Review Data Sheet

11. DOSAGE FORM: Tablet, film coated CODE: 504
12. STRENGTH/POTENCY: Ibuprofen 200 mg, Phenylephrine HCl 10 mg, Chlorpheniramine Maleate 4 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

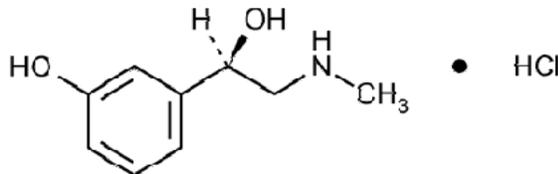
16. CHEMICAL NAMES, STRUCTURAL FORMULAE, MOLECULAR FORMULAE, MOLECULAR WEIGHTS:

Chemical Name: Benzeneacetic acid, α -methyl-4-(2-methylpropyl), (\pm)-
USAN Name: Ibuprofen
CAS: 15687-27-1
Structural Formula:



Molecular Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.28

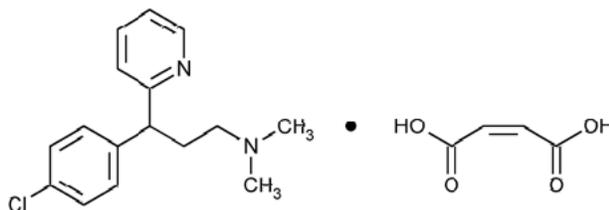
Chemical Name: Benzenemethanol, 3-hydroxy- α -[(methylamino)methyl]-,
Hydrochloride (*R*)-
USAN Name: Phenylephrine Hydrochloride
CAS: 61-76-7
Structural Formula:



Molecular Formula: $C_9H_{13}NO_2 \cdot HCl$
Molecular Weight: 203.67

CMC Review Data Sheet

Chemical Name: 2-Pyridinepropanamine, γ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1)
 USAN Name: Chlorpheniramine Maleate
 CAS Registry Number: 113-92-8
 Structural Formula:



Molecular Formula: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$
 Molecular Weight: 390.86

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	August 24, 2006	
				3	Adequate	December 7, 2007	
				3	Adequate	May 16, 2006	
				1	Adequate	January 25, 2008	
				1	Adequate	January 23, 2008	
				1	Adequate	January 15, 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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending inspection		Bogdan Kurtyka
Pharm/Tox			
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	N/A		
EA	Categorical exclusion granted (see review)	June 1, 20008	Bogdan Kurtyka
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Therefore, from a CMC perspective, this NDA is recommended for "Approval" pending satisfactory completion of cGMP inspections.

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 and Drug Substances

(1) Drug Substances

The proposed drug contains three drug substances: Ibuprofen, Phenylephrine HCl, and Chlorpheniramine Maleate. All drug substances are controlled by corresponding USP monographs, as well as listed in CFR for OTC use. The application includes Letters of Authorization from holders of (b) (4) (Ibuprofen (b) (4)), (b) (4) (Phenylephrine HCl (b) (4)), (Chlorpheniramine Maleate (b) (4)). All Drug Master Files are deemed adequate to support this application.

(2) Drug Product

(b) (4) are gray film-coated oval shaped tablets. Each tablet contains 200 mg Ibuprofen USP, 10 mg Phenylephrine Hydrochloride USP, and 4 mg Chlorpheniramine Maleate.

Inactive ingredients include Acesulfame Potassium, Carnauba Wax, Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Glyceryl Behenate, (b) (4), (b) (4), Microcrystalline Cellulose, Propyl Gallate, Pregelatinized Starch, Silicon Dioxide, Sucralose and (b) (4). With the exception of the (b) (4), film coating, and printing ink, all excipients are compendial.

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 10, 20 or 40 tablets. A one-count pouch constructed from

Executive Summary Section

(b) (4) will also be available. (b) (4)
tablets are manufactured by Wyeth Consumer Healthcare, Guayama, PR. The manufacturing process consists of (b) (4)

The drug product specification includes tests for Appearance, Ibuprofen Identity and Assay, Phenylephrine Identity and Assay, Chlorpheniramine Identity and Assay, Propyl Gallate 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, the application contains 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 20-25°C (68-77°F).

After a significant amount of PK data were collected, Wyeth discovered that the addition of antioxidant Propyl Gallate (PG) (b) (4) and decided to change the formulation. At the pre-NDA meeting, the Agency told the applicant that their request for a waiver of bioequivalence studies was “acceptable provided the in vitro dissolution profiles using multiple dissolution media are identical between the PG and non-PG products” and that the f2 test provides evidence of “sameness” ($f_2 \geq 50$). Wyeth was advised to follow the SUPAC guidance section III.B.2 case C for selection of the multiple dissolution media for the in vitro dissolution profile comparison. The dissolution data are included in the application and will be reviewed in the Pharmaceutical Development section.

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

One tablet of (b) (4) should be taken every 4 hours while symptoms persist, not to exceed 6 tablets in any 24-hour period. Medication should last less than (b) (4) days, unless directed by a doctor. The drug should be taken by adults and children above 12 years, use in children under 12 years of age should be consulted with a doctor.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of (b) (4) over the proposed shelf life (18 months) when stored as labeled.

Adequate controls for raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity, strength, quality, and purity of the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration date. Labeling is acceptable.

This NDA is recommended for “Approval” from a CMC perspective pending satisfactory completion of cGMP inspections.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Bogdan Kurtyka

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Branch Chief, Branch #3, Division 2, ONDQA

C. CC Block: entered electronically in DFS

76 Page(s) 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/

Bogdan Kurtyka
6/11/2008 04:12:15 PM
CHEMIST

Moo-Jhong Rhee
6/11/2008 05:03:13 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Nonprescription Clinical Evaluation
NDA: 22-113
Applicant: Wyeth Consumer Healthcare
Stamp Date: Sep. 25, 2007
PDUFA Date: July 25, 2008
Trademark: (b) (4)
Established Name: Ibuprofen, phenylephrine HCl and chlorpheniramine maleate
Dosage Form: Tablet
Route of Administration: Oral
Indication: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold

PAL: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

The proposed drug substances are ibuprofen, USP; phenylephrine HCl, USP; and chlorpheniramine maleate, USP. The CMC information for ibuprofen, USP is referenced to DMF (b) (4). The DMF has been reviewed multiple times and deemed adequate to support oral solid dosage forms. The CMC information for phenylephrine HCl, USP is referenced to DMF (b) (4). The DMF was most recently reviewed in October 2005 (b) (4).

The CMC information for chlorpheniramine maleate, USP is referenced to DMF (b) (4). The DMF was most recently reviewed in May 2006 (b) (4) and deemed adequate to support IND or A/NDA.

The proposed drug product, (b) (4), is an immediate-release, film-coated gray caplet printed in black ink on one side. Each caplet contains 200 mg of ibuprofen, 10 mg of phenylephrine HCl, and 4 mg of chlorpheniramine maleate with an additional (b) (4) inactive ingredients to give a total caplet weight of 495 mg. The inactive ingredients are the following: acesulfame potassium, NF; carnauba wax, NF; colloidal silicon dioxide, NF; starch corn, NF; croscarmellose sodium, NF; microcrystalline cellulose, NF; propyl gallate, NF; pregelatinized starch, NF; glyceryl behenate, NF; (b) (4); silicon dioxide, NF; sucralose, NF; (b) (4)

There are no novel excipients in the formulation.

The product is packaged in white, opaque (b) (4) blisters with child-resistant peel-push foil lidding, and a one-count white (b) (4) foil pouch. The number of caplets per blister card is ten.

The proposed to-be-marketed formulation is not the formulation investigated in the pivotal clinical study. The to-be-marketed formulation contains propyl gallate, (b) (4) in the caplets, whereas the clinical formulation does not contain propyl gallate. To support a waiver of *in-vivo* bioequivalence study, the applicant submits *in-vitro* dissolution data with f_2 analysis according to the agreement made with the FDA in the pre-NDA meeting.

The registration stability batches and clinical supplies were manufactured at the same site using the same manufacturing process and scale as that for the commercial batches. (b) (4)

Drug product stability data provided in the initial submission to support the proposed expiry period of 18 months at 20-25°C include three months of data on the to-be-marketed formulation from three primary batches stored at 25°C/60% RH, 30°C/70% RH, 30°C/75% RH, 35°C/ambient RH, and 40°C/75% RH for blisters and at 25°C/60% RH, 30°C/70% RH, 35°C/ambient RH, and 40°C/75% RH for pouches. Special stability studies provided to support the proposed product include freeze/thaw study and photostability. All registration stability batches were (b) (4) which is the proposed commercial scale.

B. Critical issues for review

- **Bio-waiver**
The proposed to-be-marketed formulation is not the formulation investigated in the pivotal clinical study. To support a waiver of *in-vivo* bioequivalence study, the applicant submits *in-vitro* dissolution data with f_2 analysis according to the agreement made with the FDA in the pre-NDA meeting. The *in-vitro* dissolution data and f_2 analysis need to be carefully reviewed to ensure that they meet bio-waiver criteria.
- **Drug product stability data**
There are only three months of data for the to-be-marketed formulation in the initial submission. It is too little to allow specification setting and projection of expiry period. A timely stability update is necessary.
- **Specificity of Methods A7277 and A7300**
Method A7277 was used in developmental and formal stability studies. The method covers all assays for the proposed drug product except dissolution test. The method validation report contains inadequate information to support the specificity of the

method. It appears that light stress was not included in the forced degradation study*. Neither were single ingredient formulations included. The applicant performed forced degradation only on a placebo (unknown formulation) and on the proposed drug product, and relied solely on peak purity assessment (by photodiode array) to determine whether there was a significant interference with the peaks of interest. There is no information regarding the sensitivity of this photodiode array approach, and how much degradation occurred upon stress.

Method A7300 is a replacement for A7277. This method is intended for commercial batches, and was not used in the formal stability studies. An equivalence study has been conducted to demonstrate that A7300 and A7277 produce equivalent results. The validation of Method A7300 mirrors that of A7277. Therefore, the same issues exist concerning specificity.

Since the method validation reports do not provide experimental details, a request should be made for the method validation protocols, especially regarding the forced degradation study and peak purity test. Specificity data need to be carefully reviewed to determine if Methods A7277 and A7300 are capable of supporting stability studies for the intended assays on active ingredients, degradants, and propyl gallate.

*It is necessary to demonstrate that the method is stability-indicating for light stressed samples since phenylephrine and chlorpheniramine are light sensitive, and a photostability study is included in the drug product stability section.

- Identity test for drug product
The proposed identity test is HPLC retention time, which is considered to be non-specific. The applicant should be requested to add a more specific identity test such as UV/Vis scan for each active ingredient.

C. Comments for 74-Day Letter

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

- Update drug product stability data for the to-be-marketed formulation.
- Provide the method validation protocols for Methods A7277 and A7300. The protocols should include experimental details for the forced degradation study and the method used to assess peak purity.

D. Recommendation:

This NDA is fileable from the CMC and quality perspective.

The major review issues of this NDA include bio-waiver, drug product stability, and method validation. Manufacturing/testing facilities are located in U.S., Puerto Rico, and (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:

(b) (4)

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

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
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
11/19/2007 04:26:42 PM
CHEMIST

Moo-Jhong Rhee
11/19/2007 04:31:38 PM
CHEMIST
Chief, Branch III