

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201803Orig1s000

CHEMISTRY REVIEW(S)



Food and Drug Administration
CDER, Office of New Drug Quality Assessment
Mail Room 2562
10903 New Hampshire Ave.
Silver Spring, Maryland 20993
(301) 796-1679
(301) 796-9747 (FAX)

MEMORANDUM

DATE: February 6, 2012

FROM: John C. Hill, Ph.D., CMC Reviewer

THROUGH: Ali Al-Hakim, Ph.D., Chief, Branch VII

TO: Melissa Furness, DARRTS File NDA 201-803

SUBJECT: Overall EES Inspection Status Acceptable

On 29-APR-2011 a Complete Response (CR) letter was issued for this NDA, citing serious deviations from cGMPs at the listed manufacturing facility. The CR letter also indicated that satisfactory resolution of these deficiencies was required before this application could be approved.

On 16-DEC-2011 the Applicant submitted a resubmission for this Application, indicating that the manufacturing deficiencies noted at the facility in question had been resolved and that this facility was now in compliance with cGMPs. In support of this claim, the overall recommendation filed in EES (see attachment) was noted as **acceptable** on 06-DEC-2011, with an overall re-evaluation date of 04-JUN-2013.

This update to the overall EES recommendation to **acceptable** resolves the outstanding cGMP violations cited in the CR letter dated 29-APR-2011. No new CMC information has been provided in this resubmission, thus the overall CMC recommendation of **approve** remains. From a CMC perspective, there are no further approvability issues with respect to this Application, the current CMC recommendation is **approve**.

Copy of EES Final Report dated 06-FEB-2012

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT					
Application:	NDA 201803/000	Action Goal:			
Stamp Date:	01-JUL-2010	District Goal:	02-MAR-2011		
Regulatory:	16-JUN-2012				
Applicant:	PFIZER CONS HLTHCARE 5 GIRALDA FARMS MADISON, NJ 07974	Brand Name:	Advil (sodium Ibuprofen 256 mg)		
Priority:	2	Estab. Name:			
Org. Code:	560	Generic Name:			
Application Comment:	PACKAGING SITE. (on 09-AUG-2010 by Y. LIU ())				
	MANUFACTURING, TESTING AND PACKAGING THE DRUG PRODUCTS. (on 09-AUG-2010 by Y. LIU ())				
FDA Contacts:	Y. LIU	Project Manager			
	S. DE	Team Leader	301-796-1664		
Overall Recommendation:	ACCEPTABLE	on 06-DEC-2011	by C. CRUZ	(HFD-323)	301-796-3254
	WITHHOLD	on 16-JUN-2011	by C. CRUZ	(HFD-323)	301-796-3254
	WITHHOLD	on 10-MAR-2011	by EES_PROD		

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT					
Establishment:	CFN: (b) (4)	FEI: (b) (4)			
	(b) (4)				
DMF No:		AADA:			
Responsibilities:	DRUG SUBSTANCE MANUFACTURER				
	(b) (4)				
Establishment Comment:					
Profile:	NON-STERILE API (b) (4)	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	03-AUG-2010				TRANZWANETZC
OC RECOMMENDATION	05-AUG-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

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

Establishment: CFN: FEI: 3007343300

PFIZER CONSUMER HEALTHCARE

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

(b) (4)

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	09-AUG-2010				LJUY
SUBMITTED TO DO	10-AUG-2010	10-Day Letter			STOCKM
ASSIGNED INSPECTION TO IB	02-SEP-2010	Product Specific			RHERNAND
DO RECOMMENDATION	10-MAR-2011			WITHHOLD	RHERNAND (b) (4)
OC RECOMMENDATION	16-JUN-2011			WITHHOLD	CRUZZ
				DISTRICT RECOMMENDATION	
SUBMITTED TO DO	06-DEC-2011	10-Day Letter			CRUZZ
PLEASE EVALUATE.					
DO RECOMMENDATION	06-DEC-2011			ACCEPTABLE	RHERNAND
ACCEPTABLE RECOMMENDATION BASED ON FIRM'S PROFILE STATUS, PLACED				BASED ON FILE REVIEW	
ACCEPTABLE ON 11/30/2011 BY COMPLIANCE. ESTABLISHMENT INSPECTION CONDUCTED					
ON 3/8/2011 AND RE-CLASSIFIED TO VAI BY COMPLIANCE.					
OC RECOMMENDATION	06-DEC-2011			ACCEPTABLE	CRUZZ
				DISTRICT RECOMMENDATION	

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

Establishment: CFN: 1119620 FEI: 1119620
 PFIZER, INC. CONSUMER HEALTHCARE
 (b) (4)
 DMF No: AADA:
 Responsibilities: (b) (4)
 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	03-AUG-2010				TRANZWANETZC
SUBMITTED TO DO	05-AUG-2010	GMP Inspection			INYARDA
ASSIGNED INSPECTION TO IB	30-AUG-2010	Product Specific			BSEEMAN
INSPECTION SCHEDULED	28-JAN-2011		28-FEB-2011		BSEEMAN
INSPECTION PERFORMED	11-FEB-2011		11-FEB-2011		BSEEMAN
NO ISSUES WERE NOTED DURING THE INSPECTION; NO FDA-483 WAS ISSUED TO THE FIRM AT THE CLOSE OF THE INSPECTION.					
DO RECOMMENDATION	16-FEB-2011			ACCEPTABLE INSPECTION	BSEEMAN
NO ISSUES WERE NOTED DURING THE INSPECTION; NO FDA-483 WAS ISSUED TO THE FIRM AT THE CLOSE OF THE INSPECTION.					
OC RECOMMENDATION	16-FEB-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: FINISHED DOSAGE PACKAGER
 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	09-AUG-2010				LIUY
SUBMITTED TO DO	10-AUG-2010	10-Day Letter			STOCKM
INSPECTION SCHEDULED	11-AUG-2010		24-SEP-2010		KOOBILAS
ASSIGNED INSPECTION TO IB	11-AUG-2010	Product Specific			KOOBILAS
DO RECOMMENDATION	03-DEC-2010			ACCEPTABLE INSPECTION	KDORAZIO
GMP AND PA INSPECTION OF 11/22 - 30/2010 WAS CLASSIFIED "NAI" WITH ACCEPTABLE PROFILES.					
OC RECOMMENDATION	03-DEC-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

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

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

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)

Establishment
Comment:

Profile: CONTROL TESTING LABORATORY
TABLETS, PROMPT RELEASE

OAI Status: NONE
NONE

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<u>Comment</u>				<u>Reason</u>	
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SUBMITTED TO DO	20-AUG-2010	10-Day Letter			STOCKM
DO RECOMMENDATION	30-AUG-2010			ACCEPTABLE BASED ON FILE REVIEW	BSEEMAN
OC RECOMMENDATION	30-AUG-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	20-AUG-2010				STOCKM
OC RECOMMENDATION	24-AUG-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

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

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

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)

Establishment
Comment:

Profile: TABLETS, PROMPT RELEASE

OAI Status: NONE

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<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-AUG-2010				LIUY
OC RECOMMENDATION	10-AUG-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

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/s/

JOHN C HILL
02/09/2012

ALI H AL HAKIM
02/09/2012



Food and Drug Administration
CDER, Office of New Drug Quality Assessment
Mail Room 2562
10903 New Hampshire Ave.
Silver Spring, Maryland 20993
(301) 796-1679
(301) 796-9747 (FAX)

MEMORANDUM

DATE: 26-APR-2011

FROM: John C. Hill, Ph.D., CMC Reviewer

THROUGH: Ali Al-Hakim, Ph.D., Chief, Branch VII

TO: NDA 201-803 File

SUBJECT: Final CMC recommendation of Complete Review for NDA 201-803, Advil

The final OC recommendation for this Application is WITHHOLD. Based on this, the final CMC recommendation for this action is Complete Review (CR).

The CMC recommendation will be re-evaluated as part of the Applicant's response to the CR letter.

Attached is a copy of the OC evaluation as entered into EES.

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

Establishment: CFN: FEI: 3007343300

PFIZER CONSUMER HEALTHCARE

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

(b) (4)

Estab. Comment:

Profile: TABLETS, PROMPT RELEASE

OAI Status: OAI ALERT

<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	09-AUG-2010				LIUY
SUBMITTED TO DO	10-AUG-2010	10-Day Letter			STOCKM
ASSIGNED INSPECTION TO IB	02-SEP-2010	Product Specific			RHERNAND
DO RECOMMENDATION	10-MAR-2011			WITHHOLD	RHERNAND

(b) (4)

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

Establishment: CFN: 1119620 FEI: 1119620
PFIZER, INC. CONSUMER HEALTHCARE

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. 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>	
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INSPECTION SCHEDULED	28-JAN-2011		28-FEB-2011		BSEEMAN
INSPECTION PERFORMED	11-FEB-2011		11-FEB-2011		BSEEMAN
NO ISSUES WERE NOTED DURING THE INSPECTION; NO FDA-483 WAS ISSUED TO THE FIRM AT THE CLOSE OF THE INSPECTION.					
DO RECOMMENDATION	16-FEB-2011			ACCEPTABLE	BSEEMAN
NO ISSUES WERE NOTED DURING THE INSPECTION; NO FDA-483 WAS ISSUED TO THE FIRM AT THE CLOSE OF THE INSPECTION.					
OC RECOMMENDATION	16-FEB-2011			ACCEPTABLE	SMITHDE
DISTRICT RECOMMENDATION					

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 DMF No: (b) (4) AADA:
 Responsibilities: (b) (4)
 Etab. Comment:
 Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

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<u>Comment</u>				<u>Reason</u>	
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SUBMITTED TO DO	10-AUG-2010	10-Day Letter			STOCKM
INSPECTION SCHEDULED	11-AUG-2010		24-SEP-2010		KDOBILAS
ASSIGNED INSPECTION TO IB	11-AUG-2010	Product Specific			KDOBILAS
DO RECOMMENDATION	03-DEC-2010			ACCEPTABLE	KDORAZIO
GMP AND PA INSPECTION OF 11/22 - 30/2010 WAS CLASSIFIED "NAI" WITH ACCEPTABLE PROFILES.				INSPECTION	
OC RECOMMENDATION	03-DEC-2010			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

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

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

DMF No: (b) (4)
Responsibilities: (b) (4)

AADA:

Estab. Comment:

Profile: CONTROL TESTING LABORATORY
TABLETS, PROMPT RELEASE

OAI Status: NONE
NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
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OC RECOMMENDATION	30-AUG-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	20-AUG-2010				STOCKM
OC RECOMMENDATION	24-AUG-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

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

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

DMF No: (b) (4)
Responsibilities: (b) (4)

AADA:

Estab. 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	09-AUG-2010				LIUY
OC RECOMMENDATION	10-AUG-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

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/s/

JOHN C HILL
04/26/2011

ALI H AL HAKIM
04/26/2011

NDA 201-803

Advil (b) (4)
(ibuprofen 200 mg provided as ibuprofen sodium 256)¹

Pfizer Consumer Healthcare

John C. Hill, Ph.D.
ONDQA/DNDQA III and OND/ODE IV/DNCE

CMC Review #2

¹ After extensive discussions within the review team and within DNCE, a request has been sent to Pfizer indicating that the nomenclature used in the drug product labeling (PI, container, packaging, etc.) be revised to read:

ibuprofen 200 mg provided as ibuprofen sodium 256 mg

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9

Chemistry Review Data Sheet

1. NDA 201-803
2. REVIEW #:2
3. REVIEW DATE: 22-FEB-2011
4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

201-803 New NDA

Document Date

30-JUN-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

(003) Stability update
(007) Response to CMC IR deficiencies
(008) Response to IR comments
(010) Labeling Response
(012) Labeling Response

Document Date

30-SEP-2010
14-JAN-2011
18-JAN-2011
03-FEB-2011
11-FEB-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer Consumer Healthcare
Address: 5 Giralda Farms
Madison, NJ 07940
Representative: Yael Gozin, Manager, Global Regulatory Affairs
Telephone: 973-660-5151

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Advil (b) (4)
b) Non-Proprietary Name (USAN): sodium ibuprofen dihydrate
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

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

Listed Reference: Motrin IB (NDA 19-012)

10. PHARMACOL. CATEGORY: NSAID (nonsteroidal anti-inflammatory drug)

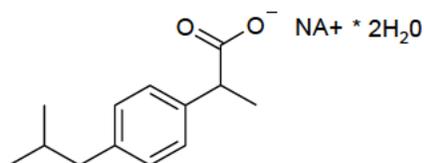
11. DOSAGE FORM: Tablet (bi-concave and caplet)

12. STRENGTH/POTENCY: 256 mg sodium ibuprofen, equivalent to 200 mg ibuprofen

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

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



Molecular Formula: $C_{13}H_{21}O_4Na$
Molecular Weight: 264.29

Chemistry Review Data Sheet

Name: Sodium 2-(4-isobutylphenyl) propionate dihydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	4	Adequate	18-FEB-2009	LOA: 19-AUG-2010
	II		4	Adequate	20-AUG-2010	LOA: 04-FEB-2010	
	III			Adequate*		LOA: 16-DEC-2009	
	III			Adequate*		LOA: 13-MAR-2009	
	III			Adequate*		LOA: 16-DEC-2009	
	III			Adequate*		LOA: 16-DEC-2009	
	III			Adequate*		LOA: 18-DEC-2009	
	III			Adequate*		LOA: 12-	

Chemistry Review Data Sheet

(b) (4)		(b) (4)	4	Adequate	Last reviewed in support of ANDA 200-794 on 14-APR-2010	FEB-2010 LOA: 03-FEB-2010
	IV		4	Adequate	24-AUG-2010	LOA: 16-JAN-2009
	IV		4	Adequate	24-AUG-2010	LOA: 04-MAY-2009

Review not needed in accordance with ONDQA review policy for container-closure systems for solid oral dosage forms.

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
Motrin IB	NDA 19-012	Ibuprofen safety and efficacy
Advil Liqui-Gels	NDA 20-402	Ibuprofen safety and efficacy
Advil Tablets, Caplets and Gel-Caplets	NDA 18-989	Ibuprofen safety and efficacy
Children's Advil Suspension	NDA 20-589 and NDA 19-833	Ibuprofen safety and efficacy in Children
Infant's Advil Drops	NDA 20812	Ibuprofen safety and efficacy in Children

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	22-FEB-2011	
Biopharm	Pending	22-FEB-2011	Albert Chen, Ph.D.
Methods Validation	Not required at this time	20-OCT-2010	John Hill, Ph.D.
Microbiology	Pending	24-AUG-2010	

The Chemistry Review for NDA 201-803

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC point of view, the application is recommended for approval pending satisfactory review conclusion from Microbiology Division and acceptable cGMP overall recommendation from Office of Compliance. Labeling issues are still under discussion with the sponsor.

A follow-up memo to file will be followed this review once these reviews are completed.

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

None identified at this time.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, sodium ibuprofen dihydrate, is manufactured under DMF (b) (4). This DMF has been reviewed and determined to be adequate from a CMC perspective. The chemical name for this compound is sodium 2-(4-isobutylphenyl) propionate dihydrate; the molecular formula is $C_{13}H_{21}O_4Na \cdot 2H_2O$ and the molecular weight: 264.29. (b) (4)

Drug Product

Advil (b) (4) tablets, 200 mg are immediate release tablets to be manufactured as either round, beige film-coated tablets, printed with black ink, containing 256 mg of sodium ibuprofen dihydrate per dosage unit (equivalent to a 200 mg dose of ibuprofen), or as beige film-coated caplet-shaped tablets, printed with black ink, containing 256 mg of sodium ibuprofen dihydrate per dosage unit (equivalent to a 200 mg dose of ibuprofen). The composition is the same for both presentations.

The marketing of Sodium Ibuprofen Tablets and Caplets, 200 mg has been proposed to occur in as many as (b) (4) different combinations of bottle types and dosage counts. The following container/closure configurations and associated tablet counts bracket the currently proposed configurations for Advil (b) (4):

Bottles:

CMC Review

Round, white, opaque, high-density polyethylene (HDPE) bottles with white (b) (4) cap with induction seal liners.



Pouch:
2 count, (b) (4) pouches.



Based on the provided real-time and supporting stability data provided, an expiry period of 24 months is granted for Advil (b) (4) tablets, 200 mg, when stored in the various proposed container/closures.

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

The maximum daily dose of Advil (b) (4) Tablets is two tablets every 4–6 hours, not to exceed six tablets in 24 hours.

C. Basis for Approvability or Not-Approval Recommendation

From CMC point of view, the application is recommended for approval pending satisfactory review conclusion from Microbiology Division and acceptable cGMP overall recommendation from Office of Compliance. Labeling issues are still under discussion with the sponsor. A follow-up memo to file will be followed this review once these reviews are completed.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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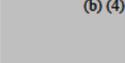
/s/

ALI H AL HAKIM

02/28/2011

Ali Al-Hakim on behalf of John Hill

NDA 201-803

Advil  ^{(b) (4)}
(sodium ibuprofen dihydrate²)

Pfizer Consumer Healthcare

John C. Hill, Ph.D.
ONDQA/DNDQA III and OND/ODE IV/DNCE



(b) (4)

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B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
S. DRUG SUBSTANCE [Sodium Ibuprofen Dihydrate, (b)(4)].....	9
P. DRUG PRODUCT [Advil (b)(4) 200 mg Tablet].....	17
A. APPENDICES	74
R. REGIONAL INFORMATION	74
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	88
A. Labeling & Package Insert	88
B. Environmental Assessment Or Claim Of Categorical Exclusion	89
III. List Of Deficiencies To Be Communicated.....	Error! Bookmark not defined.0

Chemistry Review Data Sheet

1. NDA 201-803
2. REVIEW #:1
3. REVIEW DATE: 05-NOV-2010
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

201-803 New NDA

Document Date

30-JUN-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Consumer Healthcare
Address:	5 Giralda Farms Madison, NJ 07940
Representative:	Yael Gozin, Manager, Global Regulatory Affairs
Telephone:	973-660-5151

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Advil ^{(b) (4)}
- b) Non-Proprietary Name (USAN): sodium ibuprofen dihydrate
- c) Code Name/# (ONDC only):

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

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

Listed Reference: Motrin IB (NDA 19-012)

10. PHARMACOL. CATEGORY: NSAID (nonsteroidal anti-inflammatory drug)

11. DOSAGE FORM: Tablet (bi-concave and caplet)

12. STRENGTH/POTENCY: 256 mg sodium ibuprofen dihydrate (equivalent to 200 mg ibuprofen)

13. ROUTE OF ADMINISTRATION: Oral

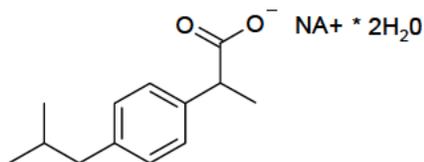
14. Rx/OTC DISPENSED: ___ Rx X OTC

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:



Molecular Formula: $C_{13}H_{21}O_4Na$

Molecular Weight: 264.29

Name: Sodium 2-(4-isobutylphenyl) propionate dihydrate

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS	
(b) (4)	II		(b) (4)	4	Adequate	20-AUG-2010	LOA: 04-FEB-2010	
	III				Adequate*		LOA: 16-DEC-2009	
	III				Adequate*		LOA: 13-MAR-2009	
	III				Adequate*		LOA: 16-DEC-2009	
	III				Adequate*		LOA: 16-DEC-2009	
	III				Adequate*		LOA: 18-DEC-2009	
	III				Adequate*		LOA: 12-FEB-2010	
					4	Adequate	Last reviewed in support of	LOA: 03-FEB-2010

Chemistry Review Data Sheet

(b) (4)		(b) (4)			ANDA 200-794 on 14-APR-2010	
	IV		4	Adequate	24-AUG-2010	LOA: 16- JAN-2009
	IV		4	Adequate	24-AUG-2010	LOA: 04- MAY-2009

Review not needed in accordance with ONDQA review policy for container-closure systems for solid oral dosage forms.

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
Motrin IB	NDA 19-012	Ibuprofen safety and efficacy
Advil Liqui-Gels	NDA 20-402	Ibuprofen safety and efficacy
Advil Tablets, Caplets and Gel-Caplets	NDA 18-989	Ibuprofen safety and efficacy
Children's Advil Suspension	NDA 20-589 and NDA 19-833	Ibuprofen safety and efficacy in Children
Infant's Advil Drops	NDA 20812	Ibuprofen safety and efficacy in Children

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	10-AUG-2010	
Pharm/Tox			
Biopharm	Pending	04-Aug-2010	Albert Chen, Ph.D.
LNC			
Methods Validation	Not required at this time	20-OCT-2010	John Hill, Ph.D.
Microbiology	Pending	24-AUG-2010	

The Chemistry Review for NDA 201-803

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

After initial review and evaluation of this application, the CMC recommendation is the application is approvable pending:

1. Adequate responses to CMC IR outlined at the end of this review
2. Finalization of the biopharm, and the microbiology consults
3. Confirmation of the USAN name, and
4. Satisfactory cGMP inspection for all sites from office of compliance

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

None identified at this time.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, sodium ibuprofen dihydrate, is manufactured under DMF (b) (4). This DMF has been reviewed and determined to be adequate from a CMC perspective. The chemical name for this compound is sodium 2-(4-isobutylphenyl) propionate dihydrate; the molecular formula is $C_{13}H_{21}O_4Na \cdot 2H_2O$ and the molecular weight: 264.29. (b) (4)

Drug Product

Advil (b) (4) tablets, 200 mg are immediate release tablets to be manufactured as either round, beige film-coated tablets, printed with black ink, containing 256 mg of sodium ibuprofen dihydrate per dosage unit (equivalent to a 200 mg dose of ibuprofen), or as beige film-coated caplet-shaped tablets, printed with black ink, containing 256 mg of sodium ibuprofen dihydrate per dosage unit (equivalent to a 200 mg dose of ibuprofen). The composition is the same for both presentations.

The marketing of Sodium Ibuprofen Tablets and Caplets, 200 mg has been proposed to occur in as many as (b) (4) different combinations of bottle types and dosage counts. The following container/closure configurations and associated tablet counts bracket the currently proposed configurations for Advil (b) (4):

Bottles:

CMC Review

Round, white, opaque, high-density polyethylene (HDPE) bottles with white (b) (4) cap with induction seal liners.



Pouch:
2 count, (b) (4) pouches.



6 months of real-time stability data have been presented which demonstrate that Advil (b) (4) tablets, 200 mg, are stable when stored in the various proposed container/closures. The applicant will be asked to provide additional stability data to support the requested expiry dating.

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

The maximum daily dose of FAI-008 200-mg Tablets is two tablets every 4–6 hours, not to exceed six tablets in 24 hours.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC perspective pending, satisfactory responses to CMC deficiencies, finalization of the consultative evaluations, confirmation of the USAN name and satisfactory conclusion of outstanding pre-approval inspections

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

JOHN C HILL
11/08/2010

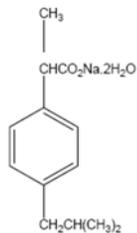
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11/08/2010

Initial Quality Assessment

Division of Nonprescription Clinical Evaluation

NDA: 201,803
Applicant: Pfizer Consumer Healthcare
5 Giralda Farms
Madison, NJ 07940
Stamp Date: 06/30/2010
PDUFA Date: 03/01/2011
Proposed Proprietary Name: Advil[®] (b)(4)
Established Name: Sodium Ibuprofen Dihydrate, 256 mg
Dosage form and strength: Tablet/Caplet; 256 mg (ibuprofen 200 mg)
Route of Administration: Oral
Indications: Pain Reliever/ Fever Reducer
CMC Lead: Swapan K De
ONDQA Fileability: Yes

Name: Sodium ibuprofen dihydrate
Molecular formula: $C_{13}H_{21}O_4Na$
Molecular Weight: 264.29



Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes

Initial Quality Assessment

Summary:

This is an e-CTD NDA application for sodium ibuprofen dihydrate 256 mg (ibuprofen 200 mg), an orally-administered propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic activity. It is known to reduce prostaglandin biosynthesis via non-selective inhibition of two isoenzymes: Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The proposed dosing is identical to that of currently marketed OTC ibuprofen free acid 200 mg (IBU), which are available in the form of tablets, caplets and liquigels. The indication of this drug product is also identical to the marketed IBU and used for temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, and the minor pain of arthritis, as well as the temporary reduction of fever.

The applicant started clinical development using sodium ibuprofen dihydrate with an IND (IND 105,341) and had a preNDA meeting with the Agency on December 15, 2009. In the meeting, CMC related topics were discussed that included stability data, USAN name and non-clinical safety issue of novel excipients in the formulation.

Drug Substance:

Sodium ibuprofen is a white crystalline powder that is freely soluble in water. The ibuprofen molecule

[REDACTED] (b) (4)

Drug Product:

[REDACTED] (b) (4)

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Initial Quality Assessment

PRODUCT QUALITY **FILING REVIEW FOR NDA (ONDQA)**

NDA Number: #201,803

Established/Proper Name:
Sodium Ibuprofen Dihydrate, 256 mg

Applicant:
Pfizer Consumer Healthcare Letter Date: 06/30/2010

Stamp Date: 06/30/2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		Looks to be in standard eCTD format.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		Appears to be
3.	Are all the pages in the CMC section legible?	X		Appears to be
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Appears to be

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Six facilities identified, all have complete addresses and FEI Numbers. However, drug product manufacturing site located at Puerto Rico address is deemed wrong.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N/A

Initial Quality Assessment

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Appears to be
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Drug product manufacturing site located at Puerto Rico address is deemed wrong. The applicant was notified through a t-con on 8/2/2010.

Initial Quality Assessment

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Appears to be.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?		X	Needs to be seen thoroughly. The applicant should provide this information.

Initial Quality Assessment

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Overview & (b) (4) diagram of manufacturing process is included.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Refer to (b) (4) DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			Refer to (b) (4) DMF (b) (4)
15.	Does the section contain controls for the DS?			Refer to (b) (4) DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Refer to (b) (4) DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

Initial Quality Assessment

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Appears to be
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		Appears to be
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Pharmaceutical development section has adequate information.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		Appears to be
25.	Does the section contain controls of the final drug product?			Appears to be
26.	Has stability data and analysis been provided to support the requested expiration date?			Appears to be
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

Initial Quality Assessment

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	Needs to be requested based on reviewers judgment.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Appears to be not needed.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Appears to be

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		It would depend on initial review by the reviewer.

Initial Quality Assessment

{See appended electronic signature page}

Swapn K De
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201803	ORIG-1	PFIZER CONSUMER HEALTHCARE	Sodium Ibuprofen, 256 mg (ibuprofen 200 mg)

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/s/

SWAPAN K DE
08/04/2010
Initial quality assessment of the NDA

ALI H AL HAKIM
08/04/2010