CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211733Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 211733
Review # 1

Drug Name/Dosage Form	**Advil Dual Action with Acetaminophen (Ibuprofen and Acetaminophen Tablets)**
Strength	**Ibuprofen (125 mg) and Acetaminophen (250 mg) Tablets**
Route of Administration	Oral
Rx / OTC Dispensed	OTC
Applicant	Pfizer, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	31-January-2019	ONDP
Response to quality IR	22 -March-2019	ONDP/OPF
Response to quality IR	03-April-2019	ONDP/OPF
Response to quality IR	24-May-2019	ONDP/OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ramsharan Mittal, Ph.D.	ONDP/DNDP-II/ Branch II
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process & facility	Yoon Oh, Ph.D.	OPF/DPAII/BranchVI
Biopharmaceutics	Hansong Chen, Ph.D.	ONDP/DB
Regulatory Business Process Manager	Teshara Bouie	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
Environmental Assessment (EA) and Labeling	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs/MAF:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	4	Adequate	N/A	None
	II			1	Adequate	04/19/2019	None
	II			1	Adequate	02/27/2019	None
	III			4	Adequate	N/A	None
	III			1	Adequate	N/A	None
	III			1	Adequate	N/A	None
	III			1	Adequate	N/A	None
	III			1	Adequate	N/A	None
	III			1	Adequate	N/A	None
	III			1	Adequate	N/A	None

C. [1] Action codes for DMF Table:

D. 1 – DMF Reviewed.
E. Other codes indicate why the DMF was not reviewed, as follows:
F. 2 –Type 1 DMF
G. 3 – Reviewed previously and no revision since last review
H. 4 – Sufficient information in application
I. 5 – Authority to reference not granted
J. 6 – DMF not available
K. 7 – Other (explain under "Comments")
L. [2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112538	Ibuprofen 125 mg/Acetaminophen 250 mg FDC tablet
IND		(b) (4)

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance	NA			

Table of Contents

Table of Contents 4

Quality Review Data Sheet ..... Executive summary 1-**3**

Executive Summary ..... Executive summary **5-9**

ASSESSMENT OF THE DRUG SUBSTANCE----------DS 1-16

2.3.S DRUG SUBSTANCE----------1-38

ASSESSMENT OF THE DRUG PRODUCT----------DP1-65

2.3.P DRUG PRODUCT----------DP1-65

ASSESSMENT OF THE PROCESS----------Process review1-25

ASSESSMENT OF THE FACILITIES ..... Process review 25-28

2.3.S DRUG SUBSTANCE ..... FR Page 25

2.3.P DRUG PRODUCT ..... FR Page 26-28

ASSESSMENT OF THE BIOPHARMACUETICS ..... BP 1-12

ASSESSMENT OF MICROBIOLOGY ..... Process review Page 23

ASSESSMENT OF ENVIRONMENTAL ANALYSIS ..... …. DP41

I.Review of Common Technical Document-Quality (Ctd-Q) Module 1Drug Product N/A

Labeling & Package Insert ..... DP 42-65

Executive Summary (NDA-211733)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the submitted application the drug substance, drug product, biopharmaceutics, process and facility sections are reviewed and found adequate to support the approval of the application (see attached reviews). The drug product is granted a 36-month shelf life when stored at USP Controlled Room Temperature ((b) (4)-25°C).

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

None

II. Summary of Quality Assessments:

This is a 505(b)(1) NDA for ibuprofen (125 mg) and acetaminophen (250 mg) combination oral tablets. The proposed indication is the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4). Facility review with "acceptable recommendation" is completed on 30 July 2019. The proposed proprietary name 'Advil Dual Action with Acetaminophen' is acceptable by DMEPA (see review dated May 02, 2019).

A. Drug Product: Quality Summary

1. **Strength:** Ibuprofen 125 mg/Acetaminophen 250 mg

2. **Description/Commercial Image:**

The proposed product is intended to have the same OTC analgesic (b) (4) indications as each individual mono-component drug product currently available within the United States. **Ibuprofen** is used to relieve minor pain (b) (4) and is a member of a class of drugs called NSAIDs which also includes aspirin and naproxen. Ibuprofen works throughout the body by inhibiting the production of compounds called prostaglandins, which have several effects, including promoting inflammation, pain (b) (4). **Acetaminophen** is an analgesic (b) (4). It is not an NSAID and does not reduce inflammation. The exact mechanism of acetaminophen has not been established, but it is thought to work in the central nervous system by activation of serotonin pathways and inhibition of prostaglandin synthesis.

The Ibuprofen 125 mg/Acetaminophen 250 mg Tablet is an immediate release yellow, film-coated, capsule-shaped tablet printed on one side in black ink. The proposed tablets are manufactured by (b) (4)

(b) (4) The container closure system for the drug product for different presentation in different sizes of bottles or pouches (HDPE bottle or white LDPE pouches) with different counts of tablets are provided in section 2.3.P.7. (b) (4)

3. Summary of Product Design

Ibuprofen (IBU) and Acetaminophen (APAP) have been formulated as a (b) (4) film-coated immediate release capsule-shaped oral tablet (caplets). The initial proof of concept efficacy study utilized 3 tablet prototypes which had fixed amounts of APAP (250 mg) combined with varying amount of IBU (b) (4)

The pharmaceutical excipients and levels that were selected for the tablet formulations were based on internal development experience and historical use with IBU containing products within Pfizer. These excipients were also commonly found in a variety of APAP tablet formulations which minimized the risk of incompatibilities.

The IBU 125 mg/APAP 250 mg tablet prototype was selected for commercial development. The formulation was modified slightly (b) (4) This formulation (WH-1477-0003) was not branded to allow for blinding of the clinical supplies. The pivotal clinical studies were conducted with this formula.

The proposed commercial formula is an immediate release yellow, film-coated, capsule-shaped tablet with a logo printed in black on one side. Except for the printed logo, the pivotal clinical formulation is (b) (4) equivalent to the registration stability and proposed commercial product (WH-1477-0005).

List of Excipients:

Carnauba wax, Colloidal silicon dioxide, Croscarmellose sodium, Ferric oxides, glyceryl dibehenate, Hypromellose (b) (4) Pharmaceutical ink (b) (4) Polydextrose, Polyethylene Glycol, Pregelatinized starch (b) (4) Titanium oxide, (b) (4)

4. Process Selection (Unit Operations Summary)

(b) (4)

(b) (4)

5. **Container Closure**:

The commercial product will be packaged in 3 types of container closure systems: (1) White, opaque high-density polyethylene (HDPE) bottles with (b) (4) caps (b) (4) 8 count (b) (4) vial with (b) (4) cap, and (3) 2 count low-density polyethylene (LDPE), (b) (4) pouch. (b) (4)

6. **Expiration Date & Storage Conditions**

The drug product is granted a 36-month shelf life when stored at USP controlled room temperature (b) (4) -25°C (68-77°F).

7. **List of co-packaged components: None**

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Advil Dual Action with Acetaminophen
Non Proprietary Name of the Drug Product	Ibuprofen 125 mg and Acetaminophen 250 mg
Non Proprietary Name of the Drug Substance	Ibuprofen and Acetaminophen
Proposed Indication(s) including Intended Patient Population	Temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4)
Duration of Treatment	Adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist.
Maximum Daily Dose	Do not take more than 6 caplets in 24 hours, unless directed by a doctor; children under 12 years: ask a doctor
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I. Ibuprofen and acetaminophen are reported as BCS class II and III drugs respectively and the biopharmaceutics reviewer concurs to that classification.
    - Drug Substance:
    - Drug Product:

2. Biowaivers/Biostudies (For NDA only)
    - Biowaiver Requests: No
    - PK studies: Yes
    - IVIVC: No

D. Novel Approaches: None

E. Any Special Product Quality Labeling Recommendations
None

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Assay method is acceptable. Impurities are monitored.
Physical stability	• Formulation Container closure • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Stable based on stability data.

Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipments • Site	2	2	2	8	Controlled with specifications
Dissolution	• Formulation Container closure • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Controlled with specifications
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	Controlled with specifications.

Life Cycle Knowledge Information related to Post-Approval Changes: None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Regarding Chemistry Manufacturing and Controls, the application may be approved.

Application Technical Lead Signature:

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

CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental Analysis

Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical criteria 21 CFR Part 25.31 (a) applicable for action on an NDA, if the action does not increase the use of active moiety. Pfizer Inc. claims that to best of the company's knowledge, no extraordinary circumstances exist.

Assessment: ***Adequate from a CMC perspective.***

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 06/26/2019.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D.; 06/26/2019 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Advil Dual Action with Acetaminophen	Acceptable by DMEPA on 4/30/2019
Established name(s)	Ibuprofen Acetaminophen	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Immediate Release Film-coated Fixed Ratio Combination Tablets 125 mg Ibuprofen & 250 mg Acetaminophen (NSAID)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A (The tablet is not scored)	N/A (The tablet is not scored)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

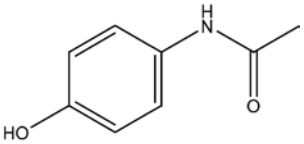
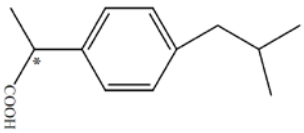
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Ready to use tablet. No special instructions for product preparation	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Acetaminophen and Ibuprofen Fixed Ratio Combination Tablet (Caplet)	Adequate
Strength(s) in metric system	250 mg Acetaminophen 125 mg Ibuprofen	There is only one strength described in the application and adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Section 3.2.P.1	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A (The tablet is not scored)	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	Advil Dual Action with Acetaminophen Ibuprofen Acetaminophen	Acceptable by DMEPA on 4/30/2019 Adequate
Dosage form(s) and route(s) of administration	Immediate Release Fix-Ratio Combination Tablet / Oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Carnauba wax Colloidal silicon dioxide Croscarmellose Sodium Ferric oxide Glycerol dibehenate Hypromellose Pharmaceutical ink Polydextrose Polyethylene glycol Pregelatinized starch Titanium dioxide	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	There is no alcohol (b) (4)	Adequate
Statement of being sterile (if applicable)	N/A	N/A

Pharmacological/ therapeutic class	Analgesic (b) (4) Pain relief Non-Steroidal Anti-inflammatory Drug (NSAID)	Adequate
Acetaminophen Chemical name, structural formula, molecular weight	IUPAC: N-(4-hydroxyphenyl)acetamide  151.16 g/mol $C_8H_9NO_2$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	pKa = 9.5 pH of a saturated aqueous solution at 25°C = 5.1 – 6.5	Adequate
Ibuprofen Chemical name, structural formula, molecular weight	IUPAC: (RS)-2-[4-(2-methylpropyl)phenyl) propanoic acid  206.26 g/mol $C_{13}H_{18}O_2$	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	1 asymmetric carbon center. Insoluble in water below pH 5.0 at both room temperature and 37°C	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	There is no misleading statement on the labels	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Solid	Adequate
Strength(s) in metric system	250 mg acetaminophen and 125 mg ibuprofen fixed-ratio combination tablet/caplet* *Capsule-Shaped Tablets	
Available units (e.g., bottles of 100 tablets)	HDPE bottles (b) (4) 18-ct/60 cc 36-ct/60 cc 72-ct/100 cc 90-ct/100 cc 144-ct/150 cc (b) (4) 162-ct/150 cc 180-ct/200 cc (b) (4) 288-ct/300 cc 144-ct/156 cc (b) (4) PP Vial 8-ct/13.4 mL Pouch (b) (4) LDPE) 2-ct/pouch	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yellow, film-coated, capsule shaped tablet with a logo printed in black ink on one side	Adequate. The description has been provided in the NDA
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	The tablet is not scored N/A	N/A

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store at 20° to 25°C (68° to 77°F)	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	The product contains no desiccant	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20° to 25°C (68° to 77°F)	The storage condition is supported by data and is acceptable.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid	N/A	N/A

statements such as “latex-free.”		
Include information about child-resistant packaging	(b) (4)	Adequate

1.2.5 Other Sections of Labeling

[There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients (b) (4) Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.]

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Pfizer, Madison, NJ 07940 USA	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Advil Dual Action with Acetaminophen is an OTC product, the Office of Nonprescription Drug Product is responsible for labeling reviews to ensure compliance with OTC labeling requirements. ONDP reviews the CMC information for consistency with information provided in the NDA.

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2 Carton Labeling

(Refer to a representative example of a proposed carton labeling in pages above)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Advil Dual Action with Acetaminophen Acetaminophen and Ibuprofen (NSAID) Capsule-Shaped Tablets	Acceptable by DMEPA on 4/30/2019 Adequate
Dosage strength	Acetaminophen 250 mg and Ibuprofen 125 mg (NSAID)	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	HDPE bottles (b) (4) 18-ct/60 cc 36-ct/60 cc 72-ct/100 cc 90-ct/100 cc 144-ct/150 cc (b) (4) 162-ct/150 cc 180-ct/200 cc (b) (4) 288-ct/300 cc 144-ct/156 cc (b) (4) PP Vial 8-ct/13.4 mL Pouch ((b) (4) LDPE) 2-ct/pouch	Adequate
"Rx only" displayed on the principal display	N/A	N/A

NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20° to 25°C (68° to 77°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Pfizer, Madison, NJ 07940 USA	Adequate
Medication Guide (if applicable)	Labels have medication guide	Adequate
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Drug product quality follows USP, ICH guidance. Acceptable.
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: ***Adequate.***

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The product labels are acceptable from a CMC perspective.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 06/26/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D., 06/26/2019

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 7/02/2019 04:38:53PM
GUID: 5050dd27000012a4c69bfc70b47660b7
Comments: Final labeling recommendations through ATL

Elise Luong

Digitally signed by Elise Luong
Date: 6/27/2019 12:49:46PM
GUID: 537253e70005b48ebb030e8b349f32e6

BIOPHARMACEUTICS

Product Background:

NDA: NDA-211733-ORIG-1

Drug Product Name / Strength: Ibuprofen (125 mg) /Acetaminophen (250 mg) FDC Tablets

Route of Administration: Oral

Applicant Name: Pfizer Inc.

Review Recommendation: **Adequate**

Review Summary:

Pfizer Inc. developed Ibuprofen (125 mg) / Acetaminophen (250 mg) FDC Tablets and submitted this application to FDA under NDA 211733 to seek approval through the 505(b)(1) regulatory pathway. The proposed drug product is intended for OTC use and indicated for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) (b) (4) muscular aches, minor pain of arthritis (b) (4)

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, and dissolution acceptance criterion.

The proposed dissolution method was reviewed and found acceptable. However, the originally proposed dissolution acceptance criterion (b) (4). The following acceptance criterion was recommended by the Agency and accepted by the Applicant:
Q= (b) (4)% in 15 minutes for both ibuprofen and acetaminophen.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 211733 for Ibuprofen (125 mg) / Acetaminophen (250 mg) FDC Tablets is **adequate** for approval. Overall, the following dissolution method and acceptance criterion have been approved:

Apparatus	USP apparatus II (Paddle)
Speed	50 rpm
Dissolution medium	50 mM Phosphate Buffer, pH 7.2
Volume	900 mL
Sampling time points	5, 10, 15, 20, and 30 min
Temperature	37 ± 0.5 °C
Sample analysis	UV analysis
Approved dissolution acceptance criterion	Q= (b) (4)% in 15 minutes for both ibuprofen and acetaminophen

List Submissions being reviewed (table):

1/31/2019	NDA 211733/Original submission
3/28/2019	eCTD-0005/Response to Biopharmaceutics Information Requests
6/21/2019	eCTD-0018/Response to Biopharmaceutics Information Requests

Highlight of Key Outstanding Issues from Last Cycle: N/A

Concise Description of Outstanding Issues: None.

BCS Designation

Reviewer's Assessment:
The Applicant reported that ibuprofen is a BCS Class II drug and acetaminophen is a BCS Class III drug. This Reviewer agreed with the Applicant on the reported BCS classification of ibuprofen and acetaminophen.

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: ***Adequate***

1. Composition of Drug Product

Table 1. Composition of Ibuprofen 125 mg/Acetaminophen 250 mg Tablet

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
				(b) (4)
Ibuprofen	Active	USP	125.00	24.33
Acetaminophen	Active	USP	250.00	48.66
Hypromellose (b) (4)				(b) (4)
Croscarmellose Sodium				
Colloidal Silicon Dioxide				
Pregelatinized Starch (b) (4)				
(b) (4)				
Glyceryl Dibehenate				
(b) (4)				
Carnauba Wax (b) (4)				
(b) (4)				

2. Dissolution method

The Applicant developed the following dissolution method for Ibuprofen (125 mg) / Acetaminophen (250 mg) FDC Tablets:

Table 2. The proposed dissolution method

Apparatus	USP apparatus II (Paddle)
Speed	50 rpm
Dissolution medium	50 mM Phosphate Buffer, pH 7.2
Volume	900 mL
Sampling time points	5, 10, 15, 20, and 30 min
Temperature	37 ± 0.5 °C
Sample analysis	UV analysis
Proposed dissolution acceptance criterion	Q= (b) (4) % in (b) (4) minutes for both ibuprofen and acetaminophen

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

(b) (4)

[redacted]

4. Dissolution data and acceptance criterion

Table 4. Lot Information of clinical and primary stability batches

Batch number	Batch size	Manufacturing site	Manufacture date	Use
1477-0003-005	(b) (4)		Mar 04, 2015	Clinical
1477-0003-006			Mar 30, 2016	Clinical
1477-0005-004			Jul 21, 2015	Primary stability

1477-0005-005	(b) (4)	Jul 22, 2015	Primary stability
1477-0005-006		Jul 22, 2015	Primary stability

Table 5. Mean ibuprofen dissolution data of clinical and primary stability lots

Lot number/Time (min)	5	10	15	20	30
1477-0003-005	94.6	99.6	100.3	100.4	100.4
1477-0003-006	88.4	94.7	96.6	97.2	97.4
1477-0005-004	96.2	100.2	100.9	101	101
1477-0005-005	88.8	97.6	99.8	100.4	100.8
1477-0005-006	93.8	98.9	100.4	100.5	100.5

Table 6. Mean acetaminophen dissolution data of clinical and primary stability lots

Figure 4. Mean ibuprofen dissolution profile comparison of clinical and primary stability lots

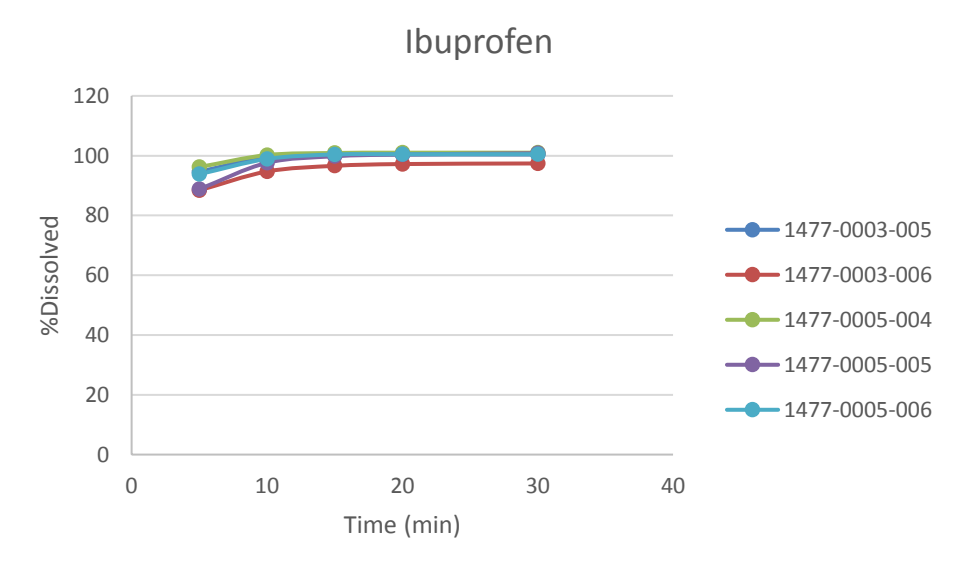
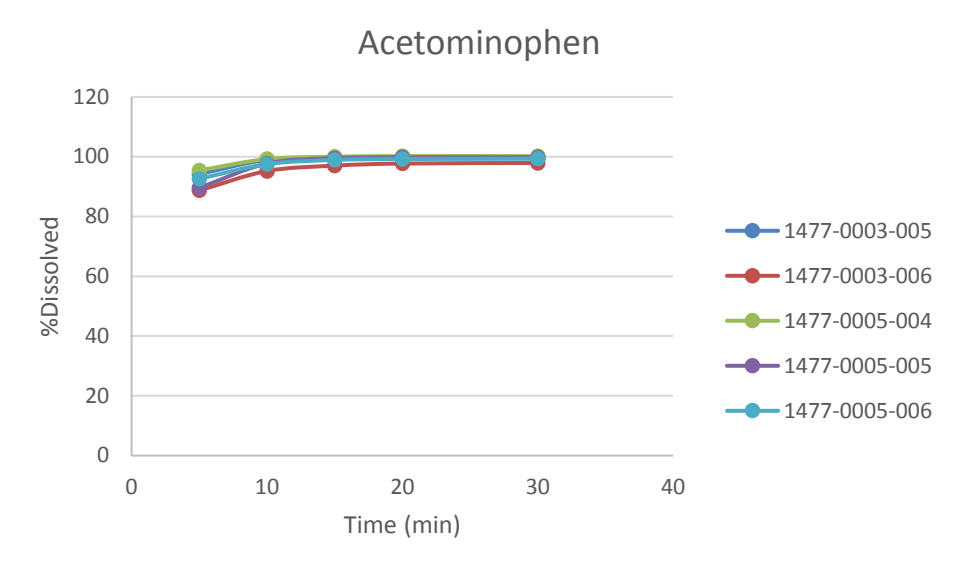


Figure 5. Mean acetaminophen dissolution profile comparison of clinical and primary stability lots



The Applicant proposed the following dissolution acceptance criterion:
Q= (b)(4)% in (b)(4)minutes for both ibuprofen and acetaminophen.

The proposed dissolution acceptance criterion (b) (4). Tables 5 and 6 show that all exhibit batches have a mean dissolution of (b) (4)% at 15 minutes for both ibuprofen and acetaminophen. The following data driven acceptance criterion was recommended by the Agency to the Applicant:
Q= (b)(4)% in 15 minutes for both ibuprofen and acetaminophen.

The above recommended dissolution acceptance criterion is appropriate. Based on the data of Clinical Lot 1477-0003-006, this Reviewer used the Division of Biopharmaceutics Automation tool to simulate the passing rate against the recommended dissolution acceptance criterion at different stages for both ibuprofen and acetaminophen. The results show that the passing rates are (b) (4) at Stage 1 and Stage 2, respectively (Tables 7 and 8).

(b) (4)

In the response to Biopharmaceutics IR II, the Applicant stated that they accepted the recommended dissolution acceptance criterion.

Application of dissolution/IVIVC in QbD

Reviewer's Assessment:

The Applicant reported that acetaminophen is a BCS Class III drug and ibuprofen is a BCS Class II drug. The Applicant did not conduct any additional studies to demonstrate if the proposed dissolution acceptance criterion is clinically relevant.

The Applicant did not report whether they conducted risk assessment to identify high or medium risk API property, formulation, and manufacturing process variables that affect CQAs.

Ibuprofen

(b) (4)

Acetaminophen

(b) (4)

Bridging of Formulations

Reviewer's Assessment: *Adequate*

The commercial formulation is the same as the one used in pivotal clinical studies except the commercial one has a logo printed in black ink on one side. Figures 4 and 5 show that the clinical lots and the commercial lots are similar on dissolution profiles because all of them dissolved more than (b) (4)% within 15 minutes.

Clinical Lot 1477-0003-006 and Clinical Lot 1477-0003-005 were manufactured at different sites. The similar dissolution profiles between these two lots provide sufficient bridge for the manufacturing site change.

Appendix I. Dissolution Data

Dissolution data of clinical lots

Lot 1477-0003-005

Vessel	Ibuprofen (% Dissolved)						Acetaminophen (% Dissolved)					
	Time (min)						Time (min)					
	0	5	10	15	20	30	0	5	10	15	20	30
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Average	0	95	100	100	100	100	0	94	99	100	100	100
Std. Dev.	N/A	1.6	1.1	1.0	0.8	0.8	N/A	1.9	1.2	1.1	1.0	1.0
%RSD	N/A	1.65	1.09	0.96	0.79	0.79	N/A	1.97	1.25	1.09	1.00	1.00

Lot 1477-0003-006

Vessel	Ibuprofen (% Dissolved)						Acetaminophen (% Dissolved)					
	Time (min)						Time (min)					
	0	5	10	15	20	30	0	5	10	15	20	30
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Average	0	88	95	97	97	97	0	89	95	97	98	98
Std. Dev.	N/A	1.3	0.7	0.7	0.7	0.8	N/A	1.2	0.8	0.6	0.8	0.8
%RSD	N/A	1.48	0.69	0.69	0.74	0.81	N/A	1.39	0.88	0.62	0.80	0.81

The dissolution data of primary stability lots:
The complete dissolution data of other primary stability lots can be located by the following link:
\\cdsesub1\evsprod\nda211733\0001\m3\32-body-data\32p-drug-prod\ibuprofen-acetaminophen-tablet\32p2-pharm-dev\pharmaceutical-development-drug-prod.pdf

Appendix II. Information Requests (IR)

Biopharmaceutics Information Request 1

After the filling review, the first Biopharmaceutics IR was sent to the Applicant on 1/10/2019. On 1/22/2019, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 1

In Module 3.2.P.2.2. Drug Product, you reported how you optimized the dissolution medium pH and rotation speed for the proposed dissolution method. However, you did not report the detailed dissolution data (individual, mean, SD, %RSD, and profiles) for Figure 3.2.P.2.2-22, Figure 3.2.P.2.2-23, and Figure 3.2.P.2.2-24. Submit the data to the Agency for review.

Applicant's response to IR 1

In support of the Agency's request, Pfizer is providing the dissolution development report, 17GTR010 "Development of Dissolution Methods (b) (4) including a Dissolution Rotation Study and Media pH Study for Ibuprofen and Acetaminophen Tablets". This report contains the requested detailed dissolution data referenced in Section 3.2.P.2.2 Drug Product.

Reviewer's comment

The response is adequate.

Biopharmaceutics Information Request 2

The second Biopharmaceutics IR was sent to the Applicant on 6/17/2019. On 6/21/2019, the Applicant responded to the second IR. The following are Biopharmaceutics IR 2, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 2

Based on the submitted in vitro dissolution profile data, the proposed dissolution acceptance criterion of "NLT (b) (4)% of the labeled amount of ibuprofen and acetaminophen dissolved in (b) (4) minutes" (b) (4) for your proposed drug product and not acceptable. The following data-driven dissolution acceptance criterion is recommended: "NLT (b) (4)% of the labeled amount of ibuprofen and acetaminophen dissolved in 15 minutes".

We request that you acknowledge your acceptance of the recommended dissolution acceptance criterion. Implement the recommended dissolution acceptance criterion for your drug product at release and on stability and update the specifications of your drug product with the revised acceptance criterion for the dissolution test, accordingly.

Applicant's response to IR 2

The Applicant stated that they accepted the recommended dissolution acceptance criterion and updated the specification tables and other relevant parts of this NDA accordingly.

Reviewer's comment
The response is adequate.

List of Deficiencies:
None.

Primary Biopharmaceutics Reviewer Name:
Hansong Chen, PharmD, Ph.D.
Biopharmaceutics Reviewer
OPQ/ONDP/DB

Secondary Reviewer Name:
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead
OPQ/ONDP/DB

Hansong Chen

Digitally signed by Hansong Chen
Date: 8/23/2019 11:20:43PM
GUID: 525d7d660003845a197a2e1682433d0d

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 8/28/2019 01:41:37PM
GUID: 50bdfe8d00003559ede66be3fd299f65

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SWAPAN K DE
09/09/2019 11:24:35 AM