CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209471Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 209471
Assessment 4

Drug Product Name	Acetaminophen 325 mg/ibuprofen 97.5 mg tablets
Dosage Form	tablet
Strength	Acetaminophen 325 mg/ibuprofen 97.5 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	AFT Pharmaceuticals Ltd
US agent, if applicable	David Zuchero, MS, JD, Highland, MD

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 37; eCTD 0036	27 Jul 21	All, new formulation submitted
Supporting document 41; eCTD 0040	1 Sep 21	Drug product
Supporting document 43; eCTD 0042	3 Nov 21	Biopharm
Supporting document 45; eCTD 0044	15 Nov 21	Process/ facilities
Supporting document 46; eCTD 0045	29 Nov 21	Drug product
Supporting document 47; eCTD 0046	7 Dec 21	Drug substance
Supporting document 49; eCTD 0048	20 Dec 21	Drug product
Supporting document 50; eCTD 0049	21 Dec 21	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeff Medwid	Donna Christner
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Yeung Chan	Jingbo Xiao

Microbiology	N/A	N/A
Biopharmaceutics	Leah Falade	Hansong Chen
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application based on drug substance, drug product, process and facilities and biopharmaceutics reviews.

The proposed shelf-life of 36 months is acceptable when stored controlled room temperature 20°–25°C (68°–77° F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed shelf-life of 36 months is acceptable when stored controlled room temperature 20°–25°C (68°–77° F).

This is the second resubmission of this NDA (submitted 27 Jul 21) and the sponsor has submitted a new formulation with all new drug substance and drug product manufacturers. New analytical methods and stability data has also been provided.

The first resubmission of this drug product was received 7 May 20. The CMC recommendation was for complete response due to a lack of inspection of a facility in (b) (4) due to the pandemic. A second complete response letter was sent to the applicant on 6 Nov 20.
This NDA was originally submitted on 1 Mar 17. CMC IQA Review 1 (dated 18 Nov 17) recommends complete response based on drug product and process deficiencies. CMC IQA Review 2 (dated 10 Dec 17) also recommends complete response with an update to withhold for facilities due to a facility becoming OAI at the very end of the first review cycle. A complete response letter was sent to the applicant on 22 Dec 17.

Proposed Indication(s)	Short term management of mild to moderate acute pain

including Intended Patient Population	
Duration of Treatment	(b) (4)
Maximum Daily Dose	12 tablets per day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

For this resubmission both drug substances DMF suppliers for this NDA were changed from the first two submissions. Both DMFs have been recently reviewed as Adequate. As a result, there are no approvability issues for the drug substance portion of this application and there are no deficiencies that need to be reported to the Applicant with respect to the drug substance portion of this application. The data is adequate to support the use of Acetaminophen and Ibuprofen in the manufacture of Combogesic (b) (4) (Acetaminophen/Ibuprofen) tablet drug product.

Drug Product: Adequate

In the current resubmission package, the Applicant has replaced their previous formulation of Combogesic tablets manufactured by (b) (4) with a reformulated Combogesic tablet manufactured by Mayne Pharma Inc., Greenville, NC, USA. The reformulated Combogesic tablets (acetaminophen 325 mg/Ibuprofen 97.5 mg) are developed as white, biconvex, capsule-shaped, film-coated tablets. The proposed reformulated Combogesic tablet manufacturing process involves (b) (4) . Adequate data has been submitted in the resubmission package and subsequent IR responses to support the proposed re-test period of (b) (4) No novel excipients are used in the proposed formulation. The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substances. The tablets are packaged in a 250 mL HDPE bottle with one white, round (b) (4) cap and (b) (4) desiccant (b) (4) to package 250 tablets. The Applicant has provided 36 months of long-term and 6 months accelerated stability data for three registration batches; no significant stability trends are observed. The stability data supports the proposed shelf-life of 36 months.

Labeling: Adequate

Manufacturing: Adequate

The drug product is Acetaminophen/ibuprofen tablet with strength of 325 mg Acetaminophen and 97.5 mg Ibuprofen. The manufacturing process includes [redacted].
Process review was deemed adequate at the end of review cycle #2.* However, both drug product formulation and commercial manufacturing facilities have changed for the third review cycle and they have been withdrawn from the current submission. During third cycle review, [redacted] have been identified as high risk unit operations. [redacted].
The drug product manufacturing facility has experience manufacturing similar immediate release tablets formulations. The firm is currently cGMP compliant and is deemed approvable at this time. Similarly, drug substance manufacturing facilities have experience manufacturing other API and intermediates by chemical synthesis and are currently cGMP compliant and are also deemed approvable at this time.

Biopharmaceutics: Adequate

The Applicant has resubmitted the NDA and reformulated its proposed drug product to be manufactured in Greenville, NC. As per SUPAC-IR, the changes in formulation and manufacturing site are considered Level 3 changes. The reformulated product is manufactured using [redacted]. A new dissolution method has been developed with the goal of [redacted]. A BE study has been conducted to compare the original formulation vs. the reformulated drug product, which is assessed by the Office of Clinical Pharmacology (OCP).
The Applicant's proposed dissolution method is acceptable. The dissolution method is not discriminatory to changes in manufacturing processes or excipients for ibuprofen. [redacted].

Microbiology (if applicable): Choose an item.

N/A

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	2 Oct 21 and 29 Oct 21	Reviewed by Jeff Medwid and Weixiang Dai
	II			1	1 Sep 21	Roger Farr

Action codes for DMF Table:
1 – DMF Reviewed.
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")

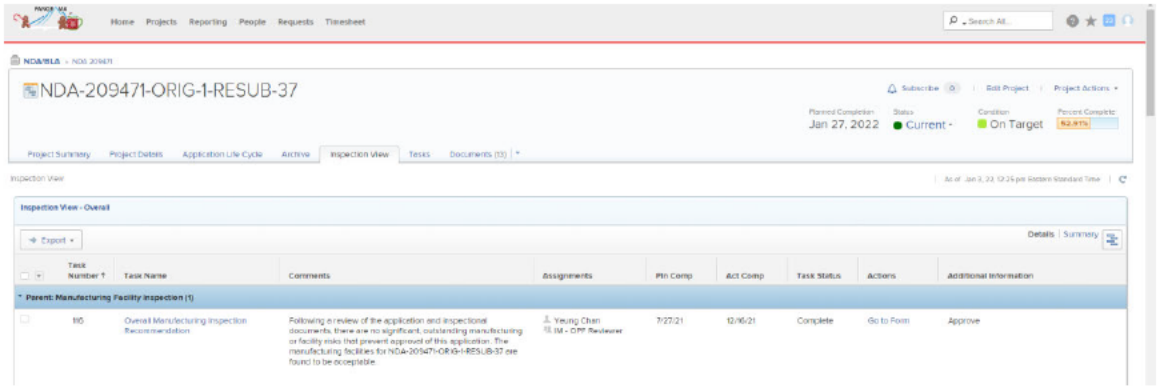
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

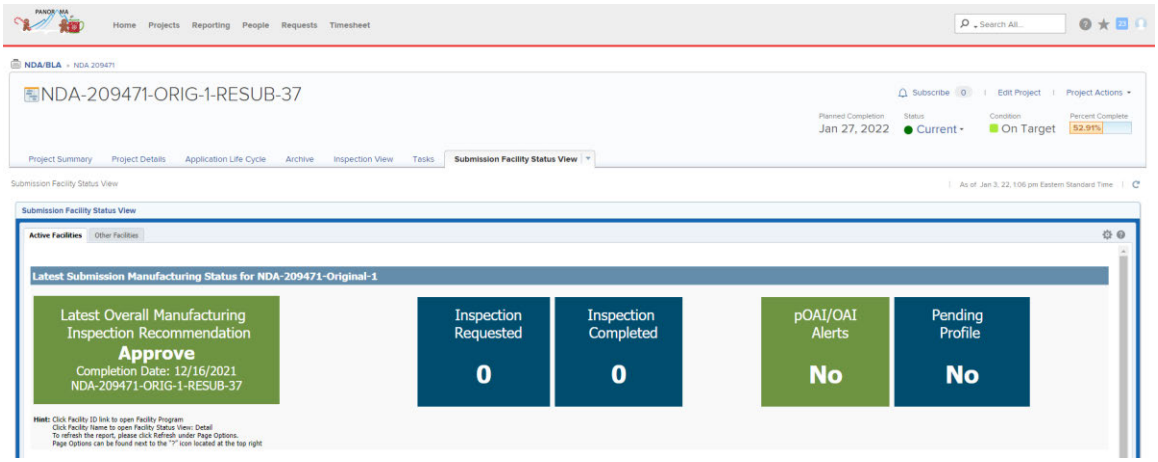
Document	Application Number	Description
NDA	021123	Ultracet tablets (acetaminophen 325 mg/ tramadol hydrochloride 37.5 mg) Janssen Pharmaceuticals
NDA	075682	Ibuprofen 800 mg Dr. Reddy Laboratories

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Screenshot of facilities showing approval taken 3 January 2022

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Projects
Reporting
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Timesheet
NDA/BLA
NDA-209471-ORIG-1-RESUB-37
Subscribe
Edit Project
Project Actions
Planned Completion
Jan 27, 2022
Status
Current
Condition
On Target
Percent Complete
52.91%
Project Summary
Project Details
Application Life Cycle
Archive
Inspection View
Tasks
Submission Facility Status View
Submission Facility Status View
Submission Facility Status View
Active Facilities
Other Facilities
Latest Submission Manufacturing Status for NDA-209471-Original-1
Latest Overall Manufacturing Inspection Recommendation
Approve
Completion Date: 12/16/2021
NDA-209471-ORIG-1-RESUB-37
Inspection Requested
0
Inspection Completed
0
pOAI/OAI Alerts
No
Pending Profile
No

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	COMBOGESIC®	
Established name(s)	(Acetaminophen/Ibuprofen) tablets for oral use	
Route(s) of administration	Oral	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	•Film-coated tablet. •Each tablet contains acetaminophen 325 mg and ibuprofen 97.5 mg	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

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)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section "COMBOGESIC® tablets with acetaminophen 325 mg and ibuprofen 97.5 mg are white, biconvex, capsule-shaped film coated tablets, debossed with the letters "CG" on one side and plain on the other side."		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Yes	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally 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	

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

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	No	Comment in working label for removal of use of (b) (4) from the label.
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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	No	Comment in working label to include molecular formula for ibuprofen.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	No	The Applicant asked to add information about solubility and other relevant physicochemical properties of acetaminophen.

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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	DMEPA comment to remove (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

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.)	No	See comment below.
If the product contains a desiccant, ensure the size and shape differ from the	Yes	

dosage form and desiccant has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	NO	The Applicant asked to “Replace (b) (4) with 20- 25°C (68°F to 77°F) and add reference to USP controlled room temperature. Include the statement “Protect from moisture and light” as appears on the carton label.”
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 statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	N.A	

1.2.5 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: Mayne Pharma Inc, 1240 Sugg Parkway, Greenville, North Carolina, 27834, United States. Distributed by: AFT Pharmaceuticals Ltd	The Applicant asked to include distributer's location.

2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal	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	
And others, if space is available	None	

Assessment of Carton and Container Labeling: *Adequate*

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Renishkumar Delvadia, PhD, 12/29/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, 12/29/2021.

Renishkumar Delvadia

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	209471-ORIG-1-RESUB-37
Drug Product Name/ Strength	Combogesic® (acetaminophen/ibuprofen) Tablets, 325 mg/97.5 mg
Route of Administration	Oral
Applicant Name	AFT Pharmaceuticals Ltd.
Therapeutic Classification/ OND Division	Non-narcotic Analgesics/ Division of Anesthesiology, Addiction, and Pain Medicine (DAAP)
LD Number	NDA 021123 for Ultracet (acetaminophen and tramadol HCl) Tablets NDA 017463 for Motrin (ibuprofen) Tablets
Proposed Indication	For the short-term management of mild to moderate acute pain
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Hansong Chen, Pharm.D., Ph.D.

REVIEW SUMMARY

AFT Pharmaceuticals Ltd. submitted NDA #209471 on 07/03/2017 under section 505(b)(2) using ULTRACET Tablets (acetaminophen/tramadol, 325 mg/37.5 mg) NDA #21123 and IBUPROFEN (ibuprofen, 800 mg) NDA #017463 as the Listed Drugs (LD). The Biopharmaceutics review was adequate[1]; however, the application status was Complete Response (CR) due to the inspection requirement of the manufacturing facility in (b) (4).

Due to the COVID pandemic hindering the conduction of the inspection, the Applicant has resubmitted the NDA and reformulated its proposed drug product to be manufactured in Greenville, NC. As per SUPAC-IR, the changes in formulation and manufacturing site are considered Level 3 changes. The reformulated product is manufactured using (b) (4). A new dissolution method has been developed with the goal of (b) (4) A BE study has been conducted to compare the original formulation vs. the reformulated drug product, which is assessed by the Office of Clinical Pharmacology (OCP).

[1] Panorama NDA 209471 Biopharmaceutics Review 11/02/2017

The Applicant's proposed dissolution method is acceptable. The dissolution method is not discriminatory to changes in manufacturing processes or excipients for ibuprofen. However, due to the new manufacturing process that (b) (4) . The following dissolution method and acceptance criterion are deemed acceptable for release and on stability:

Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criterion
USP Apparatus 2 (Paddle)	50 rpm	900 mL	37°C	Phosphate buffer, pH 5.8	Q= (b) (4)% in 15 min for acetaminophen and ibuprofen

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-209471-ORIG-1-RESUB-37 for Combogesic® (acetaminophen/ibuprofen) Tablets, 325 mg/97.5 mg is **adequate**.

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0036 (SD 37)	07/27/2021	Resubmission
0042 (SD 43)	11/03/2021	Quality Response to IR

FORMULATION

As per SUPAC-IR, the change in formulation is considered a Level 3 change for amount of (b) (4) and many excipients were added or deleted. A BE study has been conducted to compare the original formulation vs. the reformulated drug product, which is assessed by the Office of Clinical Pharmacology (OCP). The original formulation and the proposed formulation are provided below.

Table 1. Original Formulation for Combogesic® (acetaminophen and ibuprofen) Tablets, 325 mg/97.5 mg

Component	Quantity per tablet (mg)	Quality Standard	Function
(b) (4)			
Acetaminophen**	325.00	USP/Ph. Eur.	Drug substance
Ibuprofen***	97.50	USP/Ph. Eur.	Drug substance
(b) (4)	(b) (4)	USP/Ph. Eur.	(b) (4)
Microcrystalline cellulose#		USP/Ph. Eur.	
(b) (4)		USP/Ph. Eur.	
Croscarmellose sodium		USP/Ph. Eur.	
(b) (4)			
		USP/Ph. Eur.	
		In-house	
		USP/Ph. Eur.	
		USP/Ph. Eur.	
Talc		USP/Ph. Eur.	
Magnesium stearate		USP/Ph. Eur.	
(b) (4)			
(b) (4) *HPMC* (b) (4) *Hypromellose* (b) (4) *Lactose Monohydrate* *Titanium Dioxide* (b) (4) (b) (4) (b) (4)		In-house *Ph. Eur./USP/JP* *Ph. Eur./NF/JP* *Ph. Eur./USP/FCC/JP* *Ph. Eur/NF* *Ph. Eur./USP/JP/JSFA*	
(b) (4)		USP/Ph. Eur.	
(b) (4)		In-house	
Total weight of coated tablet			

Table 2. Proposed Formulation for Combogesic® (acetaminophen and ibuprofen) Tablets, 325 mg/97.5 mg

Component	Quantity per tablet (mg)	Quality Standard	Function
Dry Mixing			
Acetaminophen	325.00	USP	Drug substance
Ibuprofen	97.50	USP	Drug substance
Sodium lauryl sulfate	(b) (4)	USP-NF	(b) (4)
Microcrystalline cellulose		USP-NF	
Povidone-30		USP	
Croscarmellose sodium		USP-NF	
Lactose monohydrate		USP-NF	
(b) (4)		USP	
Magnesium stearate		USP	
(b) (4)			
(b) (4)		In-house	
		USP	
Total weight of coated tablet			
(b) (4)			

Table 3. Comparative Composition for Combogesic® (acetaminophen and ibuprofen) Tablets, 325 mg/97.5 mg

Component	Function	Original Formulation (%)	Proposed Formulation (%)	% Difference
(b) (4)				(b) (4)
Microcrystalline cellulose				
(b) (4)				
Croscarmellose sodium				
Talc				
Magnesium stearate				
(b) (4)				
Sodium lauryl sulfate				
Providone-30				
Lactose monohydrate				

DISSOLUTION

The approved dissolution method for the original formulation used 900 mL of phosphate buffer, pH (b) (4) with USP Apparatus 2 (paddle) at 50 rpm[2]. A different dissolution method was proposed in this resubmission for the reformulated Combogesic® Tablets because the original method was found to lack discriminating power when comparing the original and reformulated drug products. In response to the IR (Seq 0042), the Applicant submitted the method development reports for the new dissolution method.

It should be noted that Applicant's Maxigesic® and Rapid Maxigesic® Tablets are the higher strength of acetaminophen/ibuprofen tablets which were developed and marketed in a number of countries world-wide. The proposed drug product, Combogesic® Tablets were developed

[2] Panorama NDA 209471 Biopharmaceutics Review 11/06/2017

specifically for the US market. The original formulation of Combogesic® Tablets (b) (4) and both original dissolution methods were the same. The dissolution method development report provided in this resubmission was for the Maxigesic® and Rapid Maxigesic® Tablets. This Reviewer finds this dissolution method development report acceptable due to the following reasons:

1) The reformulated Combogesic® Tablets are designed (b) (4)
2) The original dissolution methods for the Combogesic® Tablets and the Maxigesic® Tablets are the same.
3) The API's are the same in both formulations, only differing in amounts.

Applicant's Proposed Dissolution Method and Acceptance Criterion:

Strengths/sample per vessel	Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criterion
1 × 325 mg/87.5 mg tablet	2 (paddle)	50 rpm	900 mL	37°C	Phosphate buffer, pH 5.8	Q= (b) (4)% in 15 min

Dissolution Method Development:

(b) (4)

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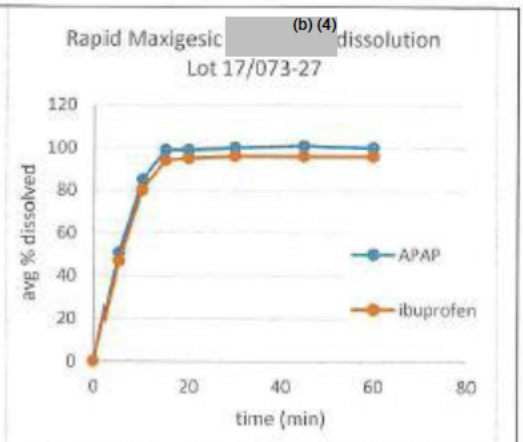
Discriminating Capability of the Dissolution Method:

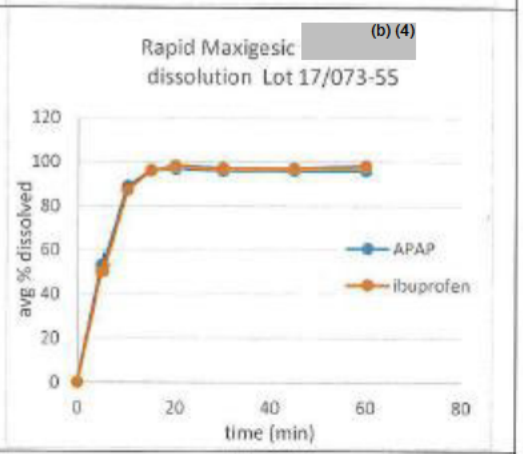
Critical Processing Parameter ((b) (4)):

The critical (b) (4) was varied which resulted in a range of particle sizes. Three lots were produced from 3 batches (b) (4) and dissolution was conducted. The batch manufactured with (b) (4) dissolves slightly faster, but this could be due to the assay values (b) (4), and not the (b) (4) process. Although this batch dissolves slightly faster, all three batches were very rapidly dissolving (>85% in 15 min). The dissolution profiles of the acetaminophen were similar to the ibuprofen. The method is not discriminating to changes in particle size and the dissolution is likely dependent on the tablet disintegration rate due to the reduced particle size of the ibuprofen.

	lot 17/073-27 (contains (b) (4) lot T1249-A, mean ibuprofen: (b) (4)			
	APAP		ibuprofen	
time	avg %	%RSD	avg %	%RSD
5	51	9.4	47	10.2
10	85	4.4	80	4.6
15	99	0.2	94	0.3
20	99	1	95	1
30	100	0.2	96	0.3
45	100	0.5	96	0.6
infinity	100	0.9	96	0.8



	lot 17/073-55 (contains (b) (4) lot T1249-D, mean ibuprofen: (b) (4)			
	APAP		ibuprofen	
time	avg %	%RSD	avg %	%RSD
5	53	8.6	50	9.4
10	89	1.9	87	2.2
15	96	1.1	96	0.9
20	97	1.6	98	1.6
30	96	1.5	97	1.6
45	96	1.9	97	1.9
infinity	96	2.1	96	2.1



	lot 17/073-41 (contains (b) (4) lot T1249F mean ibuprofen (b) (4)			
	APAP		ibuprofen	
time	avg %	%RSD	avg %	%RSD
5	64	7	63	7.6
10	93	2.1	95	2.3
15	98	1	101	0.9
20	98	0.7	102	0.7
30	98	0.7	102	0.8
45	98	0.6	102	0.6
60	99	1	102	1

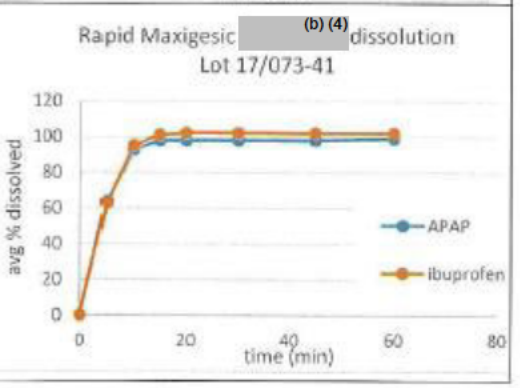


Figure 2. Dissolution Results of (b) (4) Process Changes

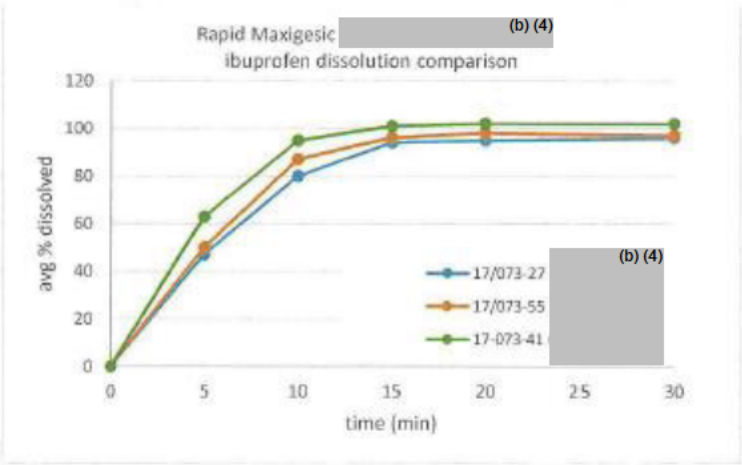


Figure 3. Dissolution Profiles of Ibuprofen

Critical Processing Parameter ((b) (4)):

Batches were manufactured (b) (4) All varied formulations had similar dissolution profiles and the dissolution was very rapidly dissolving. The method is not discriminating to changes in these manufacturing processes and the dissolution is likely dependent on the tablet disintegration rate due to the reduced particle size of the ibuprofen.

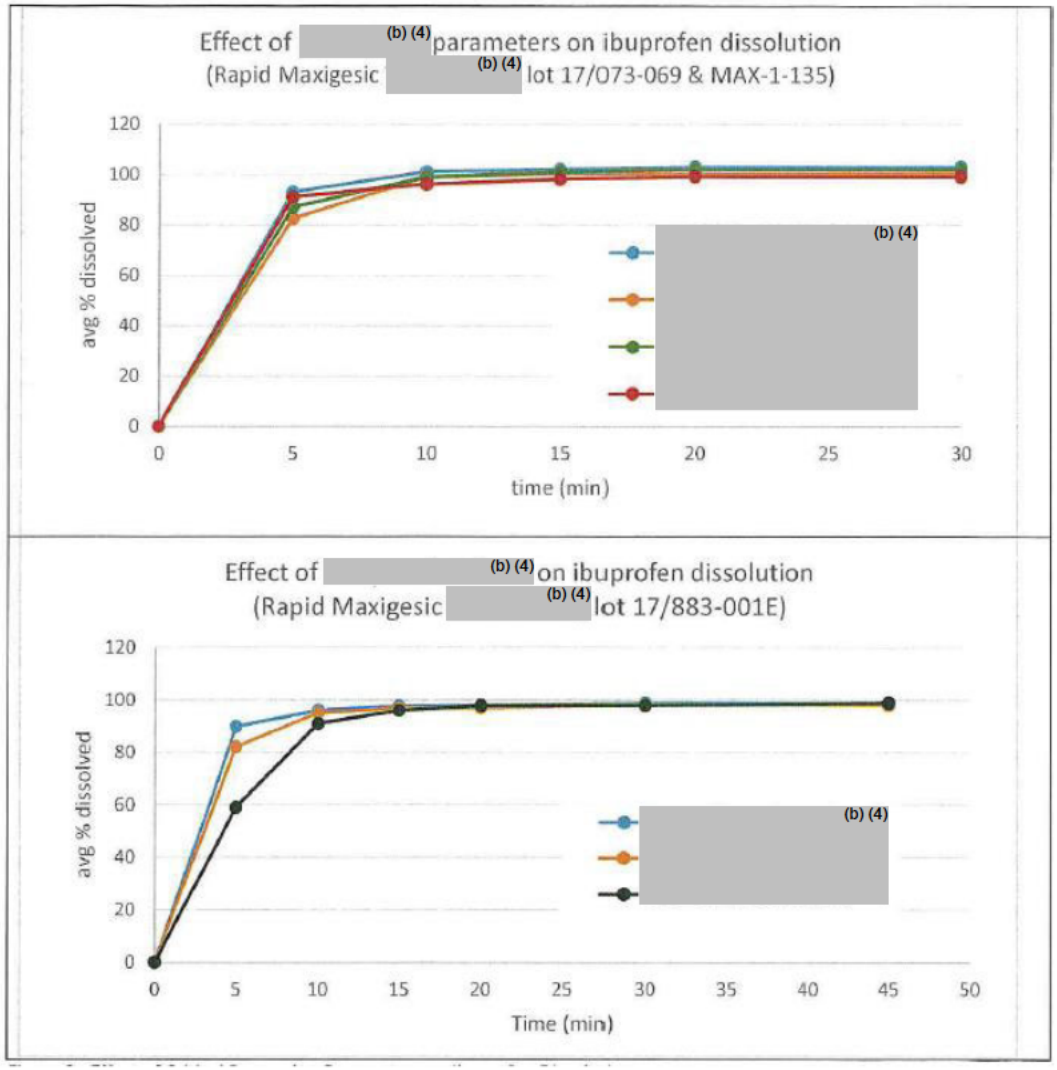


Figure 4. Effect of Critical Processing Parameters on Ibuprofen Dissolution

Excipients:

Batches were manufactured (b) (4). All varied formulations were very rapidly dissolving and have similar dissolution profiles. The method is not discriminating to changes in excipients and the dissolution is likely dependent on the tablet disintegration rate due to the reduced particle size of the ibuprofen.

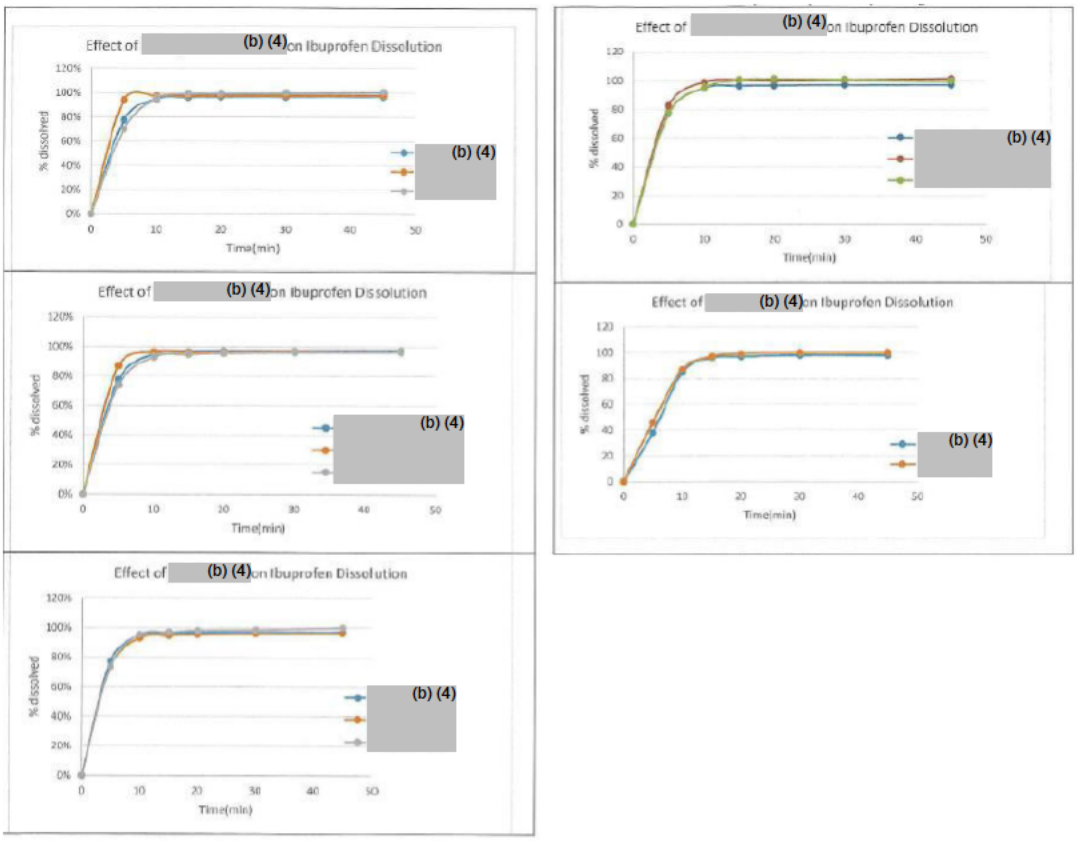


Figure 5. Dissolution Profiles of Ibuprofen for Formulation Changes

Dissolution Acceptance Criterion:

The dissolution acceptance criterion was proposed based on the data from the 3 registration batches. The dissolution profiles for acetaminophen and ibuprofen for the 3 batches are presented in below. Both API's are very rapidly dissolving (>85% in 15 min). The Applicant's proposed acceptance criterion of Q= (b) (4)% in 15 min for both components is therefore acceptable.

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Hansong Chen

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Date: 12/09/2021 08:22:23AM
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Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 1/03/2022 01:42:11PM
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VALERIE R AMSPACHER
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Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 209471
Assessment 3

Drug Product Name	Acetaminophen 325 mg/ibuprofen 97.5 mg tablets
Dosage Form	tablet
Strength	Acetaminophen 325 mg/ibuprofen 97.5 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	AFT Pharmaceuticals Ltd
US agent, if applicable	David Zuchero, MS, JD, Highland, MD

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 24; eCTD 0024	7 May 20	Drug substance, drug product, process/manufacturing, microbiology
Supporting document 28; eCTD 0027	15 Jul 20	Facilities
Supporting document 29; eCTD 0028	10 Aug 20	Drug product
Supporting document 33; eCTD 0032	21 Sep 20	Drug product
Supporting document 34; eCTD 0033	8 Oct 20	Drug substance

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeff Medwid	Donna Christner
Drug Product	Stephanie Emory	Julia Pinto
Manufacturing	Shujun Chen	Chengjiu Hu
Microbiology	Shujun Chen	Chengjiu Hu
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	

Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Stephanie Emory	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends complete response for this application. This is because of a withhold due to a facility deficiency from the process/facilities reviewer.
Drug product and drug substance recommend approval. Biopharm and microbiology remain adequate in this review cycle.

A shelf life of 36 months is acceptable when the product is stored at or below 20°–25°C (68°–77°F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The product is a white, capsule-shaped, film-coated tablet embossed with (b) (4) on one side. Tablets are packaged in (b) (4).

A shelf life of 36 months is acceptable when the product is stored at or below 20°–25°C (68°–77°F).

Although this is review 3, this is the first resubmission for this application. CMC IQA Review 1 (dated 18 Nov 17) recommends complete response based on drug product and process deficiencies. CMC IQA Review 2 (dated 10 Dec 17) also recommends complete response with an update to withhold for facilities due to a facility becoming OAI at the very end of the first review cycle.
This NDA was originally submitted on 1 Mar 17. A complete response letter was sent to the applicant on 22 Dec 17. This resubmission to respond to that CR letter was received 7 May 20.

Proposed Indication(s) including Intended Patient Population	Short term management of mild to moderate acute pain
Duration of Treatment	(b) (4)

Maximum Daily Dose	12 tablets per day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Information for two drug substances are provided in the following Type II DMFs and are incorporated by reference:

(b) (4)

Letter of Authorization (dated 16-May-2016) provided.
DMF (b) (4) reviewed as Adequate (January 10, 2020 by Barbara Scott).

(b) (4)

Letter of Authorization (dated 8 Oct 20) provided.
DMF (b) (4) reviewed as Adequate (August 7, 2019 by R. Farr).

Both DMFs have been recently reviewed as Adequate. As a result, there are no approvability issues for the drug substance portion of this application and there are no deficiencies that need to be reported to the Applicant with respect to the drug substance portion of this application. The data is adequate to support the use of Acetaminophen and Ibuprofen in the manufacture of Combogesic (Acetaminophen/Ibuprofen) tablet drug product.

Drug Product: Adequate

Several deficiencies were identified during the previous review cycle. This review focuses on the applicant's responses to the quality deficiencies communicated in the Complete Response Letter dated December 12, 2017, as well as additional stability data.

The most significant deficiencies were an incomplete drug product specification and a Total Impurities limit not supported by stability data. The applicant has submitted a complete specification with clearly delineated release and shelf-life acceptance criteria and agreed to further lower the limits for Total Impurities. The final proposed drug product specification aligns with all applicable ICH guidances, except that the second ID test is performed by TLC, in which separation is based on the same principle as the first ID test, HPLC. The applicant's commitment to develop a second ID test, as described in ICH guidance Q6A section 3.2.2.b, prior to the release of commercial batches, is considered adequate. The proposed limit of NMT (b) (4) % for (b) (4) is significantly higher than release and stability values for the registration batches. However, since the manufacturing variability is not yet known and the affected critical parameters are controlled, the applicant's commitment to tighten the acceptance criteria (b) (4) as

appropriate, based in additional batch data as it becomes available in the future, is considered adequate. Risk assessments have been provided for elemental impurities (b) (4)

Based on the stability data for 4 batches up to 60 months at long-term conditions and 6 months at accelerated, the proposed 36-month shelf-life is granted.

Labeling: Adequate

Manufacturing: Inadequate

Acetaminophen 325 mg/Ibuprofen 97.5 mg Tablet, is a film-coated tablet with drug loading at (b) (4)% and (b) (4)%, respectively. The manufacturing process includes (b) (4)
.
In this review cycle the applicant revised (b) (4) per Agency recommendation and (b) (4)
They provided clarification that full process validation will be performed on the first three commercial-scale batches ((b) (4)).

The manufacturing process is acceptable, there are no review issues with the process. The OPMA review issues are limited to facility inspection.

OPMA will recommend withhold due to a facility deficiency. This deficiency will be conveyed to the sponsor, "During a recent inspection of (b) (4), drug product manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved."

Biopharmaceutics: Adequate

Biopharmaceutics remains adequate per Okponanabofa Eradiri's entry into Panorama 13 May 2020.

Microbiology (if applicable): Adequate

Microbiology remains adequate per Shujun Chen's review dated 31 Aug 2020

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

During a recent inspection of (b) (4) , drug product manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)		3	10 January 2020	
	II			3	7 August 2019	

Action codes for DMF Table:

1 – DMF Reviewed.
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")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	21123	Ultracet tablets (acetaminophen 325 mg/ tramadol hydrochloride 37.5 mg) Janssen Pharmaceuticals
NDA	75682	Ibuprofen 800 mg Dr. Reddy Laboratories

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION (submitted in SD 23)

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	COMBOGESIC® (Acetaminophen/Ibuprofen) tablets for oral use	*Adequate*
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	•Film-coated tablet. •Each tablet contains acetaminophen 325 mg and ibuprofen 97.5 mg.	*Adequate*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	*Adequate*
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	*Adequate*

1.2 FULL PRESCRIBING INFORMATION

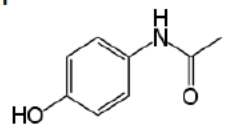
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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)	No information	*Adequate*

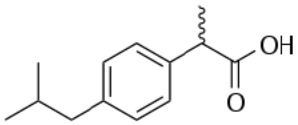
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	COMBOGESIC® tablets with acetaminophen 325 mg and ibuprofen 97.5 mg are white, coated, capsule-shaped tablets.	*Adequate*
Strength(s) in metric system		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	*Adequate*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	*Adequate*
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	*Adequate*

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	COMBOGESIC® is a combination of acetaminophen, an analgesic and antipyretic, and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID).	*Adequate*
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight	The chemical name for acetaminophen is N-acetyl-p-aminophenol. Its structural formula is:  The molecular weight of acetaminophen is 151.17.	*Adequate*
Other important chemical or physical properties (such as pKa or pH) (acetaminophen)	Acetaminophen (b) (4) occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.	*Remove the redundant statement* (b) (4)

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
Chemical name, structural formula, molecular weight (ibuprofen)	The chemical name for ibuprofen is (±)-2-(p-isobutylphenyl) propionic acid. The structural formula is:  The molecular weight of ibuprofen is 206.29.	*Adequate*
Other important chemical or physical properties (such as pKa or pH) (ibuprofen)	Ibuprofen is a white powder with a melting point of 74-77°C and is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.	*Adequate*
Dosage form(s) and route(s) of administration	COMBOGESIC® tablets contain 325 mg acetaminophen and 97.5 mg ibuprofen and are white in color.	*Add route of administration*
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	[redacted] in the tablet are [redacted] microcrystalline cellulose, [redacted], croscarmellose sodium, magnesium stearate, talc, hypromellose, lactose monohydrate, titanium dioxide, [redacted], and [redacted].	*Replace [redacted] with "inactive ingredients." List inactive ingredients in alphabetical order. Use USP names* [redacted].
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	*N/A*
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*

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	*N/A*
Statement of being sterile (if applicable)	N/A	*N/A*
If radioactive, statement of important nuclear characteristics.	N/A	*N/A*
For oral prescription drug products, include gluten statement if applicable	No information	*Adequate*
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No information	*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) Strength(s) in metric system Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	COMBOGESIC® tablets with acetaminophen 325 mg and ibuprofen 97.5 mg are white, coated, capsule-shaped tablets and are available as follows:	*Adequate*
Available units (e.g., bottles of 100 tablets)	(b) (4) [redacted]	*Concur with DMEPA revision to replace* (b) (4) [redacted] *and delete the last column.*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No information	*Adequate. The tablet is not scored.*

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

Item	Information Provided in the NDA	Assessor's Comments
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*
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at (b) (4); excursions permitted to 15 – 30°C (59 - 86°F).	*Replace (b) (4) with 20-25°C and add reference to USP controlled room temperature*
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.)	No information	*Include the statement "Protect from moisture and light" as appears on the carton label*
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."	N/A	*Adequate*
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 statements such as "latex-free."	N/A	*Adequate*
Include information about child-resistant packaging	No information	*Applicant will be asked to confirm whether child-resistant packaging is used and, if so, to include that information in this section.*

1.2.5 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: (b) (4) [redacted] Distributed by:	*Add distributor information*

1.2.6 Structured Product Labeling – product-specific information not submitted

Assessment of SPL: *Inadequate*

2.0 PATIENT LABELING

Item	Information Provided in the NDA	Assessor's Comments
Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
Manufactured by:	(b) (4) [redacted]	*Adequate*
Distributed by:	(no information provided)	*Add distributor information.*

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Item	Information Provided in the NDA		Assessor's Comments
	Carton Label	[redacted] Label	
Proprietary name, established name, and dosage form (font size and prominence	PDP: Combogesic Acetaminophen 325 mg / Ibuprofen 97.5 mg Tablets Back Panel: Each film-coated tablet contains: Acetaminophen, USP 325 mg Ibuprofen, USP 97.5 mg	Combogesic Acetaminophen 325 mg Ibuprofen 97.5 mg Tablets	*Adequate*
Dosage strength			
Route of administration	(Not present)	(Not present)	*Adequate*
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A	*Adequate*
Net contents (e.g. tablet count)	[redacted]	(Not present)	*Adequate*
"Rx only" displayed on the principal display	See label image above	N/A	*Adequate*
NDC number	[redacted]	(Not present)	*Ensure the NDC # appears on the [redacted] label*
Lot number and expiration date	See label image above	See label image above	*Adequate*
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at [redacted]. Excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Protect from moisture and light.	(Not present)	*Replace [redacted] with 20-25°C*
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	*Adequate*

Item	Information Provided in the NDA		Assessor's Comments
	Carton Label	(b) (4) Label	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A	*Adequate*
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A	*Adequate*
Bar code	See label image above	See label image above	*Adequate*
Name of manufacturer/distributor	PDP: (b) (4) Back panel: (b) (4)	(b) (4)	*Adequate*
Medication Guide (if applicable)	ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.	N/A	*Adequate*
No text on Ferrule and Cap overseal	N/A	N/A	*Adequate*
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	N/A	*Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information:

Section 11:

1. *Remove the redundant phrase* [redacted]
2. *Add route of administration*
3. *Replace* [redacted] *with "inactive ingredients." List inactive ingredients in alphabetical order. Use USP names* [redacted]

Section 16:

4. *Replace* [redacted] *with 20-25°C and add reference to USP controlled room temperature.*
5. *Include the statement "Protect from moisture and light" as appears on the carton label.*
6. *Confirm whether child-resistant packaging is used and, if so, include that information in this section.*

Manufacturing Information after Section 17:

7. *Add distributor information*

Medication Guide:

8. *Add distributor information*

Structured Product Labeling:

9. *Submit product-specific information*

Carton Label:

10. *Replace* [redacted] *with 20-25°C*

[redacted] **Label:**

11. *Ensure the NDC # is present*

Stephanie Emory

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Julia Pinto

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Shujun Chen

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Chengjiu Hu

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Valerie Amspacher

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VALERIE R AMSPACHER
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Recommendation: Complete Response

NDA 209471

Review #2

Drug Name/Dosage Form	**Acetaminophen/ibuprofenTablet/Combogesic**
Strength	**Acetaminophen 325 mg/ibuprofen 97.5mg**
Route of Administration	**Oral**
Rx/OTC Dispensed	**Rx**
Applicant	**AFT Pharmaceuticals Ltd**
US agent, if applicable	

The purpose of this review is to update the facilities recommendation of approval which was documented in the executive summary in review #1 to withhold. During a recent inspection of (b) (4), product/process controls, lab controls, and QA functions for the facility was found unacceptable. The office of process and facilities recommends a withhold for this site. The overall recommendation for CMC is a complete response. Below are the CMC deficiencies for facilities, process, and drug product. The process and drug product deficiencies are the same as in review #1.

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug product, facilities, and process, CMC will recommend a complete response for Combogesic (Acetaminophen 325 mg/Ibuprofen 97.5 mg) tablets. Drug substance, microbiology, and biopharmaceutics recommend approval.

CMC Deficiencies

Facilities

1. During a recent inspection of (b) (4), product/process controls, lab controls, and QA functions for the facility was found unacceptable for this NDA. Our field investigator observed issues at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

Drug Product

1. The example chromatograms included in the analytical procedure document are illegible and cannot be used to assess the methods.

   To address this deficiency, provide a copy of the full drug product analytical method(s) with legible representative chromatograms.

2. The total impurity results observed at release and over stability studies do not support the proposed acceptance limit of NMT (b) (4)%.

   To address this deficiency, tighten your total impurity specifications for release and stability based on the data you have provided in the NDA.

3. The drug product regulatory specifications which include all required quality attributes and their corresponding acceptance limits has not been provided. To address this deficiency, provide the final regulatory acceptance limits and tests for the release and stability of the drug product.

4. A certification is required to demonstrate that the lactose used as an excipient complies to the BSE/TSE regulations.

   To address this deficiency, provide a certification to demonstrate that the lactose used as an excipient in the drug product complies to the BSE/TSE regulations. See "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use," located at: www.fda.gov/RegulatoryInformation/Guidances/ucm125182.htm

Process

1. (b) (4)

2.

(b) (4)

3. In Section 3.2.P.3.5, you have referred to the 4 exhibit batches as validation batches, all of which are smaller than your proposed commercial batch size.

   To address this deficiency, confirm that process validation will be performed in 3 commercial-scale (b) (4) validation batches using the approved commercial process, per current FDA Guidance "Process Validation: General Principles and Practices."
   https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

Recommendation: Complete Response

NDA 209471

Review #1

Drug Name/Dosage Form	**Acetaminophen/ibuprofenTablet/Combogesic**
Strength	**Acetaminophen 325 mg/ibuprofen 97.5mg**
Route of Administration	**Oral**
Rx/OTC Dispensed	**Rx**
Applicant	**AFT Pharmaceuticals Ltd**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Sequence 1	*3/1/2017*	*OPQ Team*
Sequence 10	*6/1/2017*	*Biopharm*
Sequence 15	*8/10/2017*	*Biopharm*
Sequence 16	*9/11/2017*	*Process and Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	**Joseph Leginus**	
Drug Product	**Xiaobin Shen**	
Process	**Shujun Chen/Pei-I Chu**	
Microbiology		
Facility	**Ebern Dobbin/Christina Capacci-Daniel**	
Biopharmaceutics	**Fang Wu**	
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	**Ciby Abraham**	
Laboratory (OTR)		
ORA Lead	**Caryn McNabb/Michael Tollon**	
Environmental		

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	7/3/2017	
	Type II			Adequate	5/5/2017	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107435	
NDA	021123	
NDA	075682	

2. CONSULTS – N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug product and process, CMC will recommend a complete response for Combogesic (Acetaminophen 325 mg/Ibuprofen 97.5 mg) tablets. Drug substance, microbiology, facilities, and biopharmaceutics recommends approval.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	COMBOGESIC® is a combination of acetaminophen, an analgesic and antipyretic, and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), and is indicated for the short term management of mild to moderate acute pain.
Duration of Treatment	The recommended adult dose of COMBOGESIC® is 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.
Maximum Daily Dose	12 tablets per day.
Alternative Methods of Administration	*N/A*

Combogesic® (Acetaminophen/Ibuprofen) tablet is a combination of acetaminophen, an analgesic and antipyretic, and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) indicated for short term management of mild to moderate acute pain in adults 18 years of age and older. The white tablets are formulated to contain 325 mg acetaminophen and 97.5 mg ibuprofen with the excipients (b) (4), microcrystalline cellulose, (b) (4), croscarmellose sodium, magnesium stearate, talc, hypromellose, lactose monohydrate, titanium dioxide, (b) (4), and (b) (4)

A letter of authorization was provided for acetaminophen in DMF# (b) (4). The DMF was last reviewed on 7/3/2017 and found adequate for this application. Acetaminophen is a white crystalline powder with an approximate solubility of 1 g/70 mL in water. (b) (4)

A letter of authorization was provided for ibuprofen in DMF# (b) (4). The DMF was last reviewed on 5/5/2017 and found adequate for this application. Ibuprofen is a white to off-white fine crystalline powder that is practically insoluble in water. It has a melting point range of 75-78°C and has no identified polymorphs. (b) (4)

Acetaminophen 325 mg/ibuprofen 97.5 mg tablets are white, capsule-shaped, film-coated tablets, embossed with the letters (b) (4) on one side and plain on the other side. (b) (4)

The manufacturing process of the tablets includes (b) (4) (b) (4) (b) (4) The firm has manufactured 3 small registration stability batches (b) (4) and 1 large stability batch (b) (4) with 36 months and 12-months long-term stability data, respectively. However, we are unable to grant an expiry at this time until the deficiencies from the manufacturing process and drug product are resolved. The outstanding deficiencies for the drug product involve tightening the total impurity specifications for release and stability, requiring a BSE/TSE statement for lactose, and providing legible chromatograms for the analytical methods. For the manufacturing process, a revision for the (b) (4), and a clarification of the batch size for the validation studies are needed. Without the following information, CMC cannot recommend approval. Below are the CMC deficiencies.

CMC Deficiencies

Drug Product

1. The example chromatograms included in the analytical procedure document are illegible and cannot be used to assess the methods.

   To address this deficiency, provide a copy of the full drug product analytical method(s) with legible representative chromatograms.

2. The total impurity results observed at release and over stability studies do not support the proposed acceptance limit of NMT (b) (4)%.

   To address this deficiency, tighten your total impurity specifications for release and stability based on the data you have provided in the NDA.

3. The drug product regulatory specifications which include all required quality attributes and their corresponding acceptance limits has not been provided.

To address this deficiency, provide the final regulatory acceptance limits and tests for the release and stability of the drug product.

4. A certification is required to demonstrate that the lactose used as an excipient complies to the BSE/TSE regulations.

   To address this deficiency, provide a certification to demonstrate that the lactose used as an excipient in the drug product complies to the BSE/TSE regulations. See "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use," located at: www.fda.gov/RegulatoryInformation/Guidances/ucm125182.htm

Process

1 (b) (4)

2

3. In Section 3.2.P.3.5, you have referred to the 4 exhibit batches as validation batches, all of which are smaller than your proposed commercial batch size.

   To address this deficiency, confirm that process validation will be performed in 3 commercial-scale ((b) (4) validation batches using the approved commercial process, per current FDA Guidance "Process Validation: General Principles and Practices." https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

B. Final Risk Assessment (see Attachment)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

NDA 209471
Table of Contents

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

BIOPHARMACEUTICS

NDA: 209471

Drug Product Name/Strength: Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg) Tablets

Route of Administration: Oral

Applicant Name: AFT pharmaceuticals

Submission:

AFT pharmaceuticals is submitting an NDA, Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg) under section 505(b)(2) using ULTRACET Tablets (acetaminophen 325 mg/ tramadol hydrochloride 37.5 mg), NDA No. 21123 and IBUPROFEN (Ibuprofen 800 mg), NDA No. 75682 as the listed drugs. The formulation of acetaminophen 325 mg/ibuprofen 97.5 mg tablets was developed (b) (4) of an existing, successfully marketed, higher strength combination product (acetaminophen 500 mg/ibuprofen 150 mg), no changes to the physicochemical and biological properties of such a product were anticipated.

The primary support for the safety and efficacy of COMBOGESIC® is based on the results of the double-blind study, AFT-MX-6, entitled "Maxigesic® 325 Acute Dental Pain Study: A multicentre double-blind, placebo-controlled, randomized, parallel group comparison of the effects of Maxigesic® 325 versus paracetamol, ibuprofen and placebo in participants with moderate to severe pain from removal of at least two third molars." In addition to this pivotal study, four bioavailability and pharmacokinetic studies are also included for the COMBOGESIC® product in Module 5.3.1.1 (AFT-MX-9 to evaluate the comparative oral bioavailability of single dose of ibuprofen 97.5 mg tablets and FDC 325/97.5 tablets, AFT-MX-10 to evaluate food effect, AFT-MX-13a and AFT-MX-13b to evaluate dose normalized pharmacokinetic parameters of FDC 325/97.5 with the listed drugs Ultracet® (acetaminophen 325 mg +tramadol HCl 37.5 mg) and IBUTM (ibuprofen 800 mg) in the fasted state and fed state).

Review Summary: ADEQUATE

List Submissions being reviewed (table):

Submitted data	Description	Submission Date
Module 3.2.P.2 Pharmaceutical Developments	Dissolution method development part	03/01/2017

Module 3.2.P.5 Control of Drug Product	Specification	03/01/2017
Module 1.2 Cover Letters	Response to Information Request	06/01/2017 08/10/2017

We reviewed the dissolution method development and dissolution acceptance criteria/criterion in the above submissions, they were summarized below:

There is no full development report for Acetaminophen 325 mg/Ibuprofen 97.5 mg tablets. The proposed dissolution methods for Acetaminophen 325 mg/Ibuprofen 97.5 mg tablets were based on the USP monographs for Acetaminophen Tablets and Ibuprofen Tablets. Both monographs specify the use of Apparatus 2 (Paddle Apparatus), 900 mL phosphate buffer dissolution media, and a rotation speed of 50 rpm. Given the identical parameters of the two monographs, the methods were harmonized to propose one dissolution method for both active ingredients.

Based on the dissolution data shown in Table 7a and 7b for bio-batches for Acetaminophen 325 mg & Ibuprofen 97.5 mg, the proposed dissolution specification of "*NLT (b)(4)% (Q) of the labeled amount of acetaminophen dissolved in (b)(4) minutes and NLT (b)(4)% (Q) of the labeled amount of Ibuprofen dissolved in (b)(4) minutes*" is permissive for the proposed drug product. Therefore, the following data-driven dissolution acceptance criterion was recommended: "*NLT (b)(4)% (Q) of the labeled amount of acetaminophen and Ibuprofen dissolved in 15 minutes*" in the IR letter dated 07/28/2017. The Applicant accepted the recommended dissolution acceptance criterion in the response letter dated 08/10/2017 and updated the relevant parts of the NDA.

Table 1 Dissolution Method and Recommended Acceptance Criterion for Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg)

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Sampling Time	Recommended Acceptance Criterion (accepted on 08/10/2017)
USPII(Paddle)	50 rpm	900 mL	37°C	Phosphate buffer pH (b)(4)	(b)(4) minutes	Not less than (b)(4)% (Q) each of the labeled amounts of acetaminophen and ibuprofen is dissolved in 15 minutes

Concise Description Outstanding Issues Remaining: N/A

No more deficiencies to be communicated.

NDA 209471 is recommended for APPROVAL from a biopharmaceutics perspective.

BCS Designation

Not reported within the submission.

Solubility

Solubility testing over the physiological pH range was not included as part of the submission.

Acetaminophen
Soluble in boiling water and 1N sodium hydroxide, freely soluble in alcohol (refer to Module 3.2.S.1.3 General Properties of Acetaminophen)

Ibuprofen
Practically insoluble in water, very soluble in alcohol, in methanol, in acetone and in chloroform, slightly soluble in ethyl acetate (refer to Module 3.2.S.1.3 General Properties of Ibuprofen)

Permeability

Experimental permeability data were not provided.

Reviewer's Assessment: Adequate. The two drug substances, acetaminophen and ibuprofen, used in the formulation of the finished drug product are both well-known substances with a long history of well-tolerated use.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

1. Drug Product Composition Information

Combogesic® (Acetaminophen 325 mg/ibuprofen 97.5 mg tablets) was developed as film-coated tablets, embossed with the letters '(b) (4)' on one side and plain on the other side. The composition is shown in Table 2.

Table 2: Composition of Combogesic® (Acetaminophen 325 mg/ibuprofen 97.5 mg) tablets

Component	Quantity per tablet (mg)	Quality Standard	Function
(b) (4)			
Acetaminophen**	325.00	USP/Ph. Eur.	Drug substance
Ibuprofen***	(b) (4)	USP/Ph. Eur.	Drug substance
(b) (4)		USP/Ph. Eur.	(b) (4)
Microcrystalline cellulose#		USP/Ph. Eur.	
(b) (4)		USP/Ph. Eur.	
Croscarmellose sodium		USP/Ph. Eur.	
(b) (4)			
		USP/Ph. Eur.	
		In-house	
		USP/Ph. Eur.	
		USP/Ph. Eur.	
Talc		USP/Ph. Eur.	
Magnesium stearate		USP/Ph. Eur.	
(b) (4)			
(b) (4) *HPMC* (b) (4) *Hypromellose* (b) (4) *Lactose Monohydrate* *Titanium Dioxide* (b) (4) (b) (4) (b) (4)		In-house *Ph. Eur./USP/JP* *Ph. Eur./NF/JP* *Ph. Eur./USP/FCC/JP* *Ph. Eur/NF* *Ph. Eur./USP/JP/JSFA*	
(b) (4)		USP/Ph. Eur.	
(b) (4)		In-house	
Total weight of coated tablet			

2. Information about USP in vitro dissolution testing method for Acetaminophen FDC and Ibuprofen monograph

There is no USP monograph for Acetaminophen and Ibuprofen Tablets. There are USP monographs for acetaminophen tablets and ibuprofen tablets independently. The USP dissolution

method and acceptance criteria for Acetaminophen tablets in its monograph is shown in the following table.

Table 3 USP Monograph Acetaminophen Tablets - Dissolution Testing Method and Tolerance

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Sampling Time	Tolerances
II (paddle)	50 rpm	900 mL	37°C ± 0.5°C	pH 5.8 phosphate buffer	30 minutes	Not less than 80% (Q) of the labeled amounts of acetaminophen ($C_8H_9NO_2$) is dissolved

The USP dissolution method and tolerance for Ibuprofen Tablets in its Monograph is shown in the following table.

Table 4 USP Monograph Ibuprofen Tablets - Dissolution Testing Method and Tolerance

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Sampling Time	Approved Acceptance Criterion
II (paddle)	50 rpm	900 mL	37°C ± 0.5°C	pH 7.2 phosphate buffer	60 minutes	NLT 80% (Q) of the labeled amount of ibuprofen ($C_{13}H_{18}O_2$) is dissolved

3. Dissolution Method

The proposed dissolution method (refer to page 1 in Module 3.2.P.5.1 Specifications) was shown in Table 5:

Table 5. Proposed In Vitro Dissolution Testing Method

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Sampling Time
II (paddle)	50 rpm	900 mL	37°C	pH (b) (4) phosphate buffer	(b) (4)

A complete dissolution method development report was not provided. Therefore, the following comment was conveyed to the Applicant in #1 IR dated 05/16/2017:

- *Provide justification on the suitability of your proposed dissolution method for the combined drug product, Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg). Provide data and justification to support your selection of the proposed in vitro dissolution testing method as the optimal test for your combined product (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, sink conditions, etc.).*

Summary of Applicant's response dated 06/01/2017:

The proposed dissolution methods for Acetaminophen 325 mg/Ibuprofen 97.5 mg tablets were based on the USP monographs for Acetaminophen Tablets and Ibuprofen Tablets. Both monographs specify the use of Apparatus 2 (Paddle Apparatus), 900 mL phosphate buffer dissolution media, and a rotation speed of 50 rpm. Given the identical parameters of the two monographs, the methods were harmonized to propose one dissolution method for both active ingredients.

A differing parameter between the two USP monographs was that of the pH of the dissolution medium. The monograph for Acetaminophen Tablets specified a pH of 5.8, whereas the Ibuprofen Tablets monograph specified a pH of 7.2. Previous development dissolution testing (for a similar product of the sponsor's, Acetaminophen 500 mg/Ibuprofen 150 mg tablets) had demonstrated no differences in the solubility of acetaminophen at pH 5.8 and 7.2. Given the known poor solubility of ibuprofen in low pH conditions, the pH for the harmonized dissolution method for Acetaminophen/Ibuprofen tablets was set at pH (b) (4).

Reviewer's comment: The Applicant's response is acceptable.

3.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

Refer to the Applicant's responses dated 06/01/2017.

3.2 What data are available to support the discriminating power of the method?

Not included in the submission. The proposed dissolution methods for Acetaminophen 325 mg/Ibuprofen 97.5 mg tablets were based on the USP monographs for Acetaminophen Tablets and Ibuprofen Tablets.

3.3 Is the proposed dissolution/release method biorelevant? What data including but not limited to IVIVC are available to support this claim?

There is no information included in the submission to indicate that the in vitro dissolution testing method is biorelevant. There is no data suggesting the dissolution method and acceptance criterion can qualify a BE batch.

3.4 Overall assessment on dissolution method

Based on the above assessment, the in vitro dissolution testing method is ADEQUATE.

4. Dissolution Acceptance Criterion

The Applicant proposed dissolution acceptance criteria are shown in Table 6.

Table 6. The proposed dissolution acceptance criteria for Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg)

Amount of Acetaminophen Dissolved	Amount of Ibuprofen Dissolved
NLT (b)(4)% (Q) at (b)(4) minutes	NLT (b)(4)% (Q) at (b)(4) minutes

According to the Applicant, the specifications have been set in accordance with the specifications set in the USP monographs for Acetaminophen tablets and Ibuprofen tablets (Refer to Module 3.2.P.5.6 Justification of Specifications)

4.1 What are the dissolution data of the bio-batches used in the pivotal clinical trial?

BAD 1201 was used in three pivotal clinical trials (AFT-MX-6, AFT-MX-9 and AFT-MX-10).

Clinical Efficacy & Safety study (AFT-MX-6) was conducted for comparison of the effects of FDC 325/97.5 versus Acetaminophen 325 mg, Ibuprofen 97.5 mg and placebo in participants with moderate to severe pain.

Four bioavailability and pharmacokinetic studies were included for the COMBOGESIC® product in Module 5.3.1.1 (AFT-MX-9 to evaluate the comparative oral bioavailability of single dose of ibuprofen 97.5 mg tablets and FDC 325/97.5 tablets, AFT-MX-10 to evaluate food effect, AFT-MX-13a and AFT-MX-13b to evaluate dose normalized pharmacokinetic parameters of FDC 325/97.5 with the listed drugs Ultracet® (acetaminophen 325 mg +tramadol HCl 37.5 mg) and IBUTM (ibuprofen 800 mg) in the fasted state and fed state).

The dissolution data of Batch BAD 1201 was requested in IR#1 dated 05/16/2017.

- *Provide mean, individual, CV% (RSD) of the dissolution data for bio-batch (Batch BAD 1201).*

Summary of the Applicant's response dated 06/01/2017

Dissolution profiles used for Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg) used in the pivotal clinical trials are presented in Table 7a and 7b.

Table 7a. Individual Dissolution Profile Results for Acetaminophen (Batch BAD1201)

Sr. No.	5 min	10 min	15 min	30 min
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	79	96	101	102
Min	(b) (4)			
Max				
%RSD	2.6	0.6	1.3	0.7

Table 7b. Individual Dissolution Profile Results for Ibuprofen (Batch BAD1201)

Sr.No.	5 min	10 min	15 min	30 min
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	75	93	98	101
Min	(b) (4)			
Max				
%RSD	2.9	0.7	1.9	0.8

Based on the dissolution data shown in Table 7a and 7b for the bio-batche for Acetaminophen 325 mg & Ibuprofen 97.5 mg, the proposed dissolution specification of "NLT (b)(4)% (Q) of the labeled amount of acetaminophen dissolved in (b)(4) minutes and NLT (b)(4)% (Q) of the labeled amount of Ibuprofen dissolved in (b)(4) minutes" is too permissive for the proposed drug product. Therefore, the following data-driven dissolution acceptance criterion is recommended: "*NLT (b)(4)% (Q) of the*

labeled amount of acetaminophen and Ibuprofen dissolved in 15 minutes". The IR comment was communicated to the Applicant in the Information Request IR#2 dated 07/28/2017.

Summary of responses dated 08/10/2017

The batch release and stability specifications, and corresponding analytical procedures, have been updated in line with the FDA's recommendation. The amended specifications and analytical procedures were enclosed in Modules 3.2.P.5.1 and 3.2.P.5.2.

Reviewer's comment:

The Applicant's accepted the Agency's recommended dissolution acceptance criterion, which is acceptable.

Bridging of Formulations

Reviewer's Assessment:

1. Bridging between to-be-marked formulation and bio-batch used in the pivotal clinical trials

Batch BAD 1201 was used in three pivotal clinical trials (AFT-MX-6, AFT-MX-9 and AFT-MX-10).

The proposed maximum commercial batch size is (b) (4) (Refer to Module 3.2.P.3.2 Batch Formula), which is (b) (4) (Batch No. BAD1201, (b) (4) (refer to 3.2.P.5.4 Batch Analysis). Therefore, no bridging data is needed.

2. Bridging between to-be-marked formulation (debossed) and tablets used in the pivotal clinical trials (plain)

The following IR was conveyed in IR#1 dated 05/16/2017

- *Submit the dissolution profile similarity testing results (obtained with appropriate statistics, e.g., f2 values) comparing the debossed tablets and the tablets (plain) used in the pivotal clinical trials.*

Summary of responses dated 06/01/2017

The dissolution profiles for plain tablets (Batch BAD1202) and debossed tablets (Batch 059(1454)144) are highly similar (shown in Table 8a and 8b). All tablets tested dissolved more than 85% of the label amount of the active ingredients in 15 minutes, therefore, in line with US and ICH biopharmaceutics guidance, the calculation of f_2 is unnecessary.

Table 8a Comparative dissolution profile of Acetaminophen for Acetaminophen and Ibuprofen Tablets (Plain batch BAD 1202 vs debossed Batch 059(1454)144)

Product Name	Acetaminophen and Ibuprofen Tablets 325/97.5mg	Acetaminophen and Ibuprofen Tablets 325/97.5mg
Mfg By	(b) (4)	
B.No	BAD1202	059(1454)144
Mfd.Date	Feb-2012	Oct- 2016
Exp. Date	Jan-2014	Sep-2018
A.R.No	GVL1200697	ARD/FP/2016/3810

Sr. No.	Time points (mins)	% Drug Release (Acetaminophen) BAD1202	% Drug Release (Acetaminophen) 059(1454)144
1		(b) (4)	
2			
3			
4			
5			

Table 8b Comparative dissolution profile of Ibuprofen for Acetaminophen and Ibuprofen Tablets (Plain batch BAD 1202 vs debossed Batch 059(1454)144)

Product Name	Acetaminophen and Ibuprofen Tablets 325/97.5mg	Acetaminophen and Ibuprofen Tablets 325/97.5mg
Mfg By	(b) (4)	
B.No	BAD1202	059(1454)144
Mfd.Date	Feb-2012	Oct- 2016
Exp. Date	Jan-2014	Sep-2018
A.R.No	GVL1200697	ARD/FP/2016/3810

Sr. No.	Time points (mins)	% Drug Release(Ibuprofen) BAD1202	% Drug Release(Ibuprofen) 059(1454)144
1		(b) (4)	
2			
3			
4			
5			

Reviewer's comment: *The Applicant's response is acceptable.*

List of Communicated Deficiencies:

Biopharmaceutics Comments for IR #1:

1. Provide justification on the suitability of your proposed dissolution method for the combined drug product, Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg). Provide data and justification to support your selection of the proposed in vitro dissolution testing method as the optimal test for your combined product (i.e., selection of the

equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, sink conditions, etc.).

2. Provide mean, individual, CV% (RSD) of the dissolution data for bio-batch (Batch BAD 1201).
3. Provide dissolution similarity comparison (f2 test) for your debossed tablets and the tablet (plain) used in the pivotal clinical trials.

The above deficiency was communicated to the Applicant on 05/16/2017 and the Agency received the Applicant's responses on 06/01/2017. The responses are acceptable.

Biopharmaceutics Comments for IR #2:

1. Based on the submitted in vitro dissolution data for the lot used in the pivotal clinical study, the proposed dissolution specification of "NLT (b) (4)% (Q) of the labeled amount of acetaminophen dissolved in (b) (4) minutes and NLT (b) (4)% (Q) of the labeled amount of ibuprofen dissolved in (b) (4) minutes" is permissive for the proposed drug product, Combogesic® (Acetaminophen 325 mg & Ibuprofen 97.5 mg). Therefore, the following data-driven dissolution acceptance criterion is recommended for batch release and stability test: "*NLT (b) (4)% (Q) of the labeled amount of acetaminophen and ibuprofen dissolved in 15 minutes*". Update the relevant parts in your NDA submission accordingly.

The above deficiency was communicated to the Applicant on 07/28/2017 and the Agency received the Applicant's responses on 08/10/2017. The responses are acceptable.

There are no more deficiencies for NDA 209471 from a biopharmaceutics perspective.

Primary Biopharmaceutics Reviewer Name and Date:

Fang Wu, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drugs Products

Date: 10/23/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Kimberly Raines, Ph. D.
Secondary Biopharmaceutics Reviewer
& Branch Chief (acting)
Division of Biopharmaceutics
Office of New Drugs Products

Date: 10/27/2017

Fang Wu

Digitally signed by Fang Wu
Date: 10/27/2017 11:40:48AM
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Kimberly Raines

Digitally signed by Kimberly Raines
Date: 11/02/2017 02:41:25PM
GUID: 508da6fd000284a73fdbe11d01b3132f

Ciby Abraham

Digitally signed by Ciby Abraham
Date: 12/10/2017 09:56:21AM
GUID: 512518c000026e22966a3bf7c15f7809