CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary Assessment 2

1. Application/Product Information

NDA Number	215320		
Applicant Name	AFT Pharmaceuticals Ltd		
Drug Product Name	Combogesic (Acetaminophen/ibuprofen)		
Dosage Form	Solution		
Proposed Strength(s)	Acetaminophen 1000 mg/Ibuprofen 300 mg in 100 mL		
NDA Classification	Type 5 – New Formulation or New Manufacturer		
Route of Administration	Intravenous		
Maximum Daily Dose	4000 mg/day acetaminophen; 1200 mg/day ibuprofen		
Rx/OTC Dispensed	Rx		
Proposed Indication	-the relief of mild to moderate pain (b) (4) (b) (4) -the management of moderate to severe pain as an adjunct to opioids		
Drug Product Description	Clear solution packed in 100 mL (b) (4) glass vials with grey (b) (4) stoppers		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20-25 ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	N/A
	Drug Product/ Labeling	Renish Delvadia	Julia Pinto

	Manufacturing	Cassandra Abellard	Tianhong (Tim) Zhou
	Biopharmaceutics	N/A	N/A
	Microbiology	N/A	N/A
	Other (specify)	N/A	N/A
	RBPM	Anika Lalmansingh / Tiecher Agosto	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 24 months is acceptable when stored at controlled room temperature: 20°–25° (68°–77° F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

CMC recommends approval for this application based on a review by drug product. Drug substance, process/facilities, and microbiology all recommended approval in the previous review cycle, see CMC IQA in Panorama and DARRTS dated 10 Jun 2022.

This is the second assessment for this NDA. The original CMC IQA dated 10 Jun 2022 recommended approval from CMC. The deficiencies that led to a complete response were related to the non-clinical review.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - N/A
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. **Life-Cycle Considerations**
   Established Conditions per ICH Q12: No
   Comments:

   Comparability Protocols (PACMP): No
   Comments:

   Additional Lifecycle Comments:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 28; eCTD 0027	17 Apr 2023	Drug product, facilities

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/s/

VALERIE R AMSPACHER
09/26/2023 11:51:43 AM

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RECOMMENDATION

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

NDA 215320
Assessment 1

Drug Product Name	Acetaminophen 1000 mg/Ibuprofen (as sodium dihydrate) 300 mg in 100 mL Solution
Dosage Form	Solution for injection
Strength	Acetaminophen 1000 mg/Ibuprofen (as sodium dihydrate) 300 mg
Route of Administration	intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	AFT Pharmaceuticals Ltd
US agent, if applicable	David Zuchero, MS, JD

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0000	31 Aug 21	All, original submission
Supporting document 5; eCTD 0004	16 Dec 21	Microbiology
Supporting document 7; eCTD 0006	10 Jan 22	Process/facilities
Supporting document 10; eCTD 0009	18 Feb 22	Microbiology
Supporting document 11; eCTD 0010	18 Mar 22	Process/facilities
Supporting document 14; eCTD 0013	28 Mar 22	Drug substance
Supporting document 16; eCTD 0015	28 Apr 22	Process/facilities
Supporting document 17; eCTD 0016	4 May 22	Drug product
Supporting document 18; eCTD 0017	16 May 22	Drug product

Supporting document 18; eCTD 0017	25 May 22	Drug product
Supporting document 23; eCTD 0022	31 May 22	Drug product
Supporting document 24; eCTD 0023	1 June 22	Drug product
Supporting document 25; eCTD 0024	6 Jun 22	Drug product
Supporting document 26; eCTD 0025	6 Jun 22	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Katie Duncan	Gaetan Ladouceur
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Yuesheng Ye	Tianhong (Tim) Zhou
Microbiology	Eric Adeeku	Paul Dexter
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

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	17 Jul 20	Reviewed by Fred Burnett
	II			1	29 Mar 22	Reviewed by Katharine Duncan

(b) (4)	III	(b) (4)	4		
	III		4		

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
IND	124213	
NDA	021123	Ultracet
NDA	075682	Ibuprofen

2. CONSULTS

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

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this drug product based on reviews by drug substance, drug product, process/facilities and microbiology.

The proposed shelf-life of 24 months is acceptable when stored at controlled room temperature: 20°–25° (68°–77° F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Acetaminophen 1000 mg/Ibuprofen 300 mg in 100 mL solution for infusion is a sterile solution suppled in 100 mL glass vials closed with a (b) (4) grey stopper and sealed with aluminium caps.

The proposed shelf-life of 24 months is acceptable when stored at controlled room temperature: 20°–25° (68°–77° F).

Proposed Indication(s) including Intended Patient Population	relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary
Duration of Treatment	acute
Maximum Daily Dose	4000 mg/day acetaminophen; 1200 mg/day ibuprofen
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The CMC information for the acetaminophen drug substance is cross-referenced to DMF (b) (4) This DMF was last reviewed by Friedrich Burnett, Ph.D. in support of NDA (b) (4) on 20-Jul-20 and found to be adequate. The retest period is (b) (4) when stored at (b) (4)

The CMC information for ibuprofen sodium dihydrate is cross-referenced to DMF (b) (4) DMF (b) (4) was reviewed by Katharine Duncan, Ph.D. in support of this NDA on 29-Mar-22 and found to be adequate. The retest period is (b) (4) when stored at (b) (4)
The NDA is recommended for approval from the perspective of drug substance quality.

Drug Product: Adequate

All the excipients used in the proposed formulation are of USP/NF grade. The excipients are within the inactive ingredient database (IID) limit for the intravenous route of administration (calculated based on maximum daily dose of 400 mL per the proposed label). 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 proposed container closures are routinely used for the storage of intravenous solution.

The extractable and leachables analytical methods and studies are adequate from the CMC perspective. The Applicant has provided 36 months of long-term and intermediate stability data for three registration stability batches, and 24 months of long-term and intermediate stability data for two registration stability batches; 6 months of accelerated stability data are provided for all five registration batches. The Applicant has adequately justified the proposed drug product specification and validated respective analytical methods. Overall, the stability data supports the proposed shelf-life of 24 months.

Labeling: Adequate

Manufacturing: Adequate

The manufacturing process includes the following unit operations:

(b) (4)

The proposed commercial manufacturing facilities include: 1) Two manufacturers for the two drug substances, 2) One drug product manufacturing, primary packaging, finish product release and stability testing, and 3) no contract testing lab. They are all acceptable for the proposed function.

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

(b) (4)

The submission is recommended for approval.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**

		H, M, or L		Acceptable or Not Acceptable	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Assay (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Uniformity of Dose (Fill Volume/ deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Appearance (Color/ turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

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

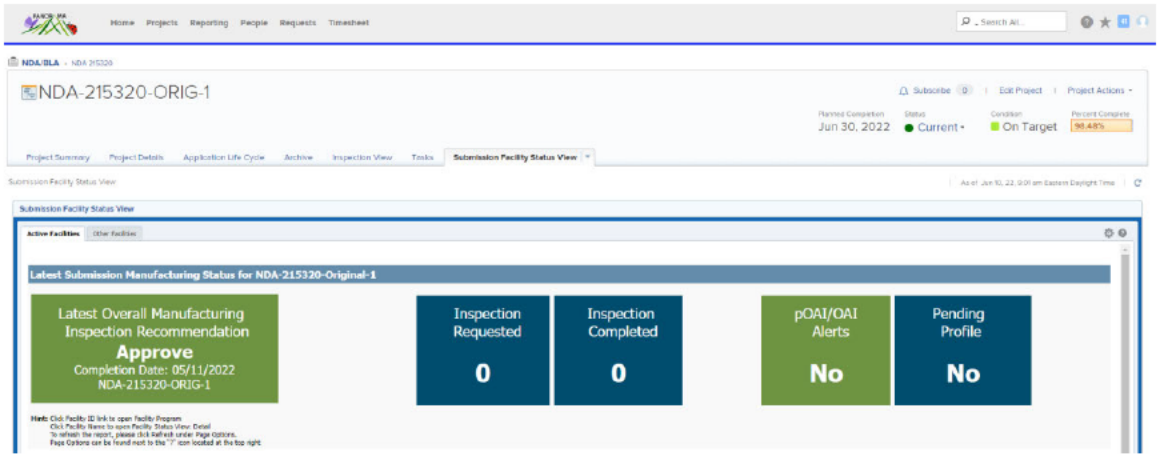
5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

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

Screenshot showing approval of facilities (taken 10 Jun 22)



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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The CMC label comments for package insert (PI) are populated in the working PI document. The changes recommended are also summarized in this review document.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	COMBOGESIC IV	Acceptable
Established name(s)	(acetaminophen and ibuprofen) injection	Acceptable
Route(s) of administration	for intravenous use.	Acceptable to OPQ
Dosage Forms and Strengths Heading in Highlights Proposed (b) (4) [redacted] Change to: "Injection: 1,000 mg/100 mL (10 mg/mL) of acetaminophen and 300 mg/100 mL (3 mg/mL) of ibuprofen in single-dose vial"		
Summary of the dosage form(s) and strength(s) in metric system.	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		See "Change to" above. The correct package type term is single dose.

pharmacy bulk package and imaging bulk package.		

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)		None

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section (b) (4) **Change to** "Injection: 1,000 mg/100 mL (10 mg/mL) of acetaminophen and 300 mg/100 mL (3 mg/mL) of ibuprofen in a clear, colorless solution in single-dose vial."		
Available dosage form(s)		
Strength(s) in metric system		
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.		See "change to" above. The correct package type term is single-dose.

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Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)		No. Comment is added to working PI
Dosage form(s) and route(s) of administration		No. Comment is added to working PI
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		Comment added to working PI for equivalency statement for ibuprofen.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		Yes
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.		Not included; Comment added to working PI asking Applicant to include both qualitative (list of ingredients) and quantitative information (e.g., amounts) for all inactive ingredients except those added to adjust pH or tonicity or water for injection.
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)		Not included.
Pharmacological/ therapeutic class		Not included for Ibuprofen; information added in working PI
Chemical name, structural formula, molecular weight		Structural formula not included for both APIs; comment added to the working PI asking sponsor to include the information about structural formula and physicochemical properties of each API.
If radioactive, statement of important nuclear characteristics.		

Other important chemical or physical properties (such as pKa or pH)		No. Comment added to working PI asking the Applicant to include pH of solution and osmolality information

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"	None	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Proposed

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)		Pack of 10 vials
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		NDC number is missing. Description of vial (i.e, clear vial etc) not included; Comments added to the working PI.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally 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.		Not included; "Single-dose" vial added to the working PI

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.)		Also add “protect from heat.” in the working PI
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
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		Change to “Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].”
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 Other Sections of Labeling

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: S.M. Farmaceutici SRL, Zona Industriale, 85050 Tito (PZ), Italy Packed by: S.M. Farmaceutici SRL, Zona Industriale, 85050 Tito (PZ), Italy Distributed by: TBD Name and location of business (street address, city, state and zip code)	Acceptable.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate
There are comments that will be conveyed to the applicant. This is acceptable.

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

IR comments for container (vial) label:

1. Change the established name to “(acetaminophen and ibuprofen) injection”.
2. Revise [redacted] (b) (4) ” to “For intravenous infusion only”.
3. Change [redacted] (b) (4) to “1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)”. Place the strength immediately below the established name.
4. Include “Single-dose vial”
5. Include “Protect from heat”
6. Change [redacted] (b) (4) to “Each 100 mL singe-dose vial contains: Acetaminophen 1000 mg, ibuprofen 300 mg (equivalent to xx mg of ibuprofen sodium dihydrate)…”
7. Include NDC code.
8. Change [redacted] (b) (4) to “Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]”.

3.2 Carton Labeling

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IR comments for carton:

1. Change the established name to "(acetaminophen and ibuprofen) injection".
2. Change (b) (4) to "1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)". Place the strength immediately below the established name.
3. Revise (b) (4) to "For intravenous infusion only".
4. Include "Single-dose vial"
5. Include "Protect from heat"
6. Change (b) (4) to "Each 100 mL singe-dose vial contains: … Ibuprofen 300 mg (equivalent to xx mg of ibuprofen sodium dihydrate)…"
7. Change (b) (4) to "Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]".

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence		Established name is not accurate. See the IR comment directly below screenshots on pages 9 and 10
Dosage strength		Not accurate; see IR comment directly below screenshots on pages 9 and 10
Route of administration		See IR comment
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Ibuprofen equivalency statement not included; See IR comment directly below screenshots on pages 9 and 10
Net contents (e.g. tablet count)		Yes
"Rx only" displayed on the principal display		Yes
NDC number		Not included on vial label; see IR comment directly below screenshots on pages 9 and 10
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.		See IR comment directly below screenshots on pages 9 and 10
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)		Not included singe-dose. See IR comment directly below screenshots on pages 9 and 10

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
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		N/A

Assessment of Carton and Container Labeling: see the *IR comments directly below screenshots on pages 9 and 10 for container (vial) and carton; these comments will be conveyed to the OND labeling reviewer to combine with DMEPA’s comments for sending to the Applicant.*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: IR comments and PI working label comments.

Adequate

Primary Labeling Assessor Name and Date: Renishkumar Delvadia

Secondary Assessor Name and Date (and Secondary Summary, as needed): Valerie Amspacher

Renishkumar Delvadia

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Date: 6/09/2022 04:29:06PM
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Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 6/10/2022 08:56:08AM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215320
Assessment Cycle Number	01
Drug Product Name/ Strength	Combogesic, Acetaminophen1000 mg/ibuprofen 300 mg/100 mL
Route of Administration	Intravenous
Applicant Name	AFT Pharmaceuticals Ltd
Therapeutic Classification / OND Division	Analgesic / N/A
Manufacturing Site	S.M. Farmaceutici SRL Zona Industriale 85050 Tito (PZ), Italy
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval.

Dates of Submission(s) Covered by this Review

Submit	Received	eCTD seq./Doc. #	Review Request	Assigned to Reviewer
08/31/2021	08/31/2021	#0000 / 1	N/A	09/17/2021
12/16/2021	12/16/2021	#0004 / 5	N/A	12/17/2021
02/18/2022	02/18/2022	#0009 / 10	N/A	02/24/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission.
Goal date is 02/28/2022.

Responses to the Agency's 11/26/2021 and 02/14/2022 information request letters were provided in the 12/16/2021 and 02/18/2022 submissions respectively.

Concise Description of Outstanding Issues: No outstanding issues remain.

Supporting Documents:

(b) (4) MR01.docx – Sterility assurance review of the (b) (4) that were found adequate in microbiology review dated 09/14/2020.

Select Number of Approved Comparability Protocols: 0

This review contains original information as well as responses to microbiology deficiencies conveyed to the sponsor in the Agency's information request letters dated 11/26/2021 and 02/14/2022 respectively. The most recent deficiency is italicized.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –
(section 3.2.P.1.1).

Acetaminophen 1000 mg/Ibuprofen (as sodium dihydrate) 300 mg in 100 mL Solution for Infusion is a sterile solution suppled in 100 mL glass vials closed with a stopper and sealed with aluminum caps. It is used for the relief of mild to moderate pain (b) (4) (b) (4) and for the management of moderate to severe pain as an adjunct to opioid analgesics.

Drug product composition –
(section 3.2.P.1).

Name of ingredient	Function	Formula per 100 mL	Formula per mL
Acetaminophen[1], USP	Active ingredient	1000.00 mg	10.00 mg
Ibuprofen Sodium dihydrate, USP	Active ingredient	385.00 mg[2]	3.85 mg[3]
Mannitol, USP	(b) (4)	3285.00 mg	32.85 mg
Disodium phosphate dihydrate, USP		13.0 mg	0.13 mg
Cysteine hydrochloride monohydrate, USP		25.00 mg	0.25 mg
Hydrochloric acid[4]	pH adjuster	q.s. pH 6.3 - 7.3	q.s. pH 6.3 - 7.3
Sodium hydroxide[4]	pH adjuster	q.s. pH 6.3 - 7.3	q.s. pH 6.3 - 7.3
Water for Injection, USP	(b) (4)	q.s. 100 mL	q.s. 1 mL
(b) (4)		q.s.	q.s.

[1]United States Adopted Name (USAN) for Acetaminophen
[2]Equivalent to 300 mg of ibuprofen
[3]Equivalent to 3 mg of ibuprofen
[4]Hydrochloric acid (b) (4) and Sodium hydroxide (b) (4) are used to adjust pH

Description of container closure system –
(section 3.2.P.7).

Component	Description	Manufacturer
Vials	100 mL/29 mm (b) (4) colorless glass vial	(b) (4)
Stoppers	29 mm dark grey (b) (4) stopper	
Seals	29 mm aluminum cap	

Adequate

(b) (4)

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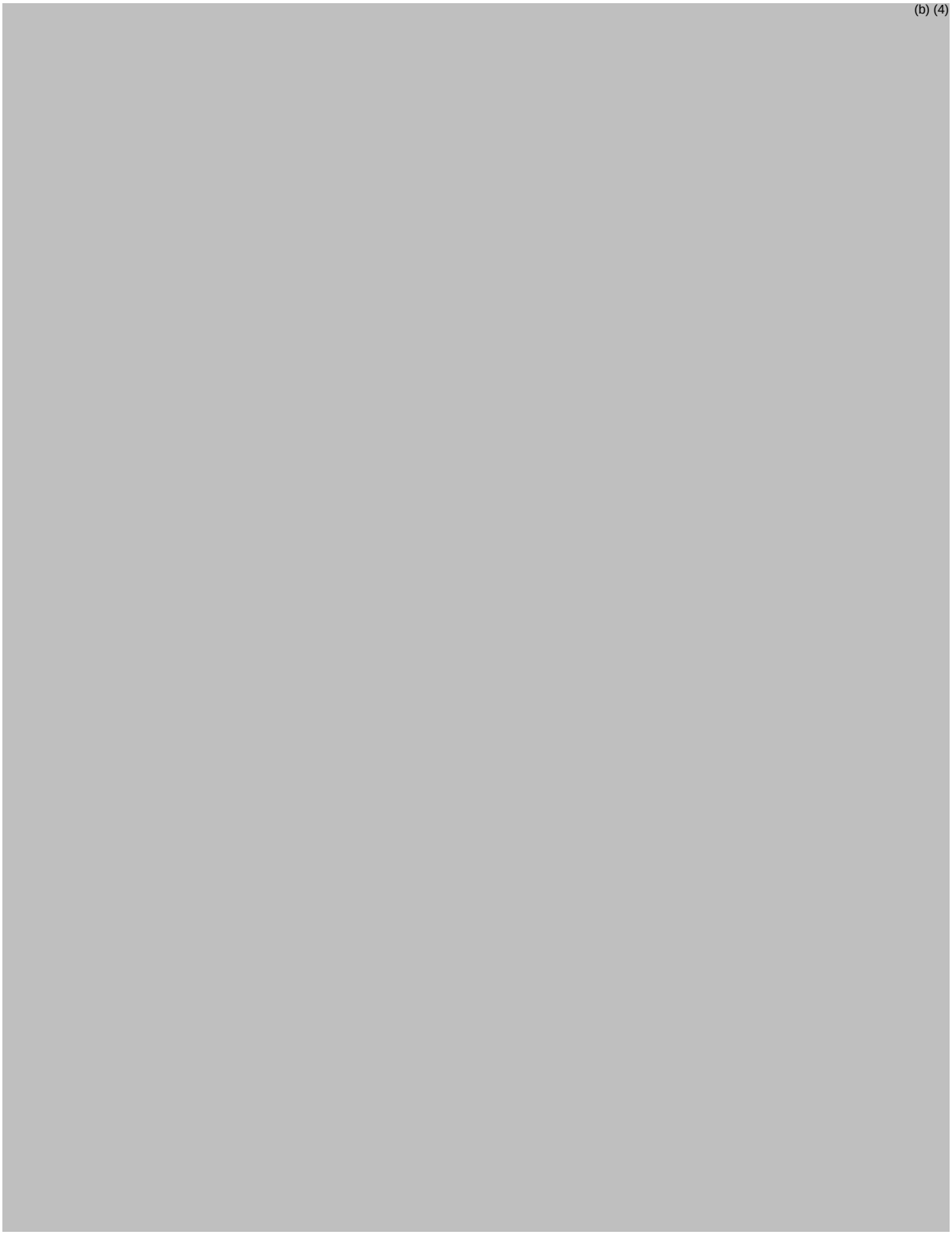
(b) (4)



Comparability Protocols

No CP was included in the application.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

Adequate

Post-Approval Commitments

None provided.

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:

Eric Adeeku, Ph.D., 03/03/2022

Secondary Assessor Name and Date

Capt. Paul Dexter, M.S., 03/02/2022

Eric Adeeku

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Date: 3/03/2022 09:17:08AM
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Paul Dexter

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Valerie Amspacher

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VALERIE R AMSPACHER
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