

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212862Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 212862
Review # 1**

Drug Name/Dosage Form	Pretomanid tablets
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	The Global Alliance for TB Drug Development
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>eCTD 025</i>	<i>05/07/2019</i>	<i>Quality</i>
<i>eCTD 022</i>	<i>04/23/2019</i>	<i>Quality</i>
<i>eCTD 021</i>	<i>04/16/2019</i>	<i>Quality</i>
<i>eCTD 020</i>	<i>04/10/2019</i>	<i>Quality</i>
<i>eCTD 017</i>	<i>04/02/2019</i>	<i>Quality</i>
<i>eCTD 013</i>	<i>03/25/2019</i>	<i>Quality</i>
<i>eCTD 012</i>	<i>03/20/2019</i>	<i>Quality</i>
<i>eCTD 011</i>	<i>03/13/2019</i>	<i>Quality</i>
<i>eCTD 005</i>	<i>02/15/2019</i>	<i>Quality</i>
<i>eCTD 003</i>	<i>02/12/2019</i>	<i>Quality</i>
<i>Original NDA</i>	<i>12/14/2018</i>	<i>All</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharon Kelly	Su Tran
Drug Product	Yong Wang	Balajee Shanmugam
Process	Aditi Thakur	Ying Zhang
Microbiology	Aditi Thakur	Ying Zhang
Facility	Aditi Thakur	Ying Zhang
Biopharmaceutics	Parnali Chatterjee	Elsbeth Chikhale

Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Englund	
Laboratory (OTR)		
ORA Lead	Caryn McNab	
Environmental	See DP Review	

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
Various	Type III	See DP review				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69580	Pretomanid IND

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Refer to DS and DP reviews			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on March 20, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

The proposed product, pretomanid tablets, is indicated in adults for the treatment of pulmonary extensively drug resistant (XDR) tuberculosis (TB) as part of a combination regimen with bedaquiline and linezolid. Pretomanid is a nitroimidazooxazine antimycobacterial drug, and was developed under IND 69580. Pretomanid tablets (200 mg) are uncoated, debossed, immediate release tablets for oral use. The applicant identified the drug as a (b) (4) drug. The product was granted orphan drug designation, QIDP designation and Fast Track Status.

As discussed under IND 69580, the clinical trial material was manufactured by (b) (4), which was issued a Warning Letter on (b) (4). The FDA requested a third-party assessment of the data generated at the API manufacturing facility to support the pivotal clinical lots. IRs were sent 6/20/2017, 7/13/2017 and 7/16/2018 regarding the audit of (b) (4). On 4/13/2018 and 10/19/2018 the FDA and sponsor met to discuss the inclusion in the NDA of the (b) (4) drug substance and drug product batches in the NDA. These meetings also discussed the introduction of (b) (4) as the commercial manufacturer of the drug substance (b) (4).

The results of a comparability study were also submitted for the batches manufactured at the different sites.

0	 Total Number of Comparability Protocols (ANDA only)

Proposed Indication(s) including Intended Patient Population	Indicated for adults as part of a combination regimen with bedaquiline and linezolid, for the treatment of pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).
Duration of Treatment	Once daily for 26 weeks
Maximum Daily Dose	200 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The drug substance, Pretomanid, is a new molecular entity. It contains one chiral center (6S), is a single isomer and the most thermodynamically stable polymorphic form is (b) (4). All DS batches manufactured at (b) (4) were confirmed to be (b) (4). The drug substance (DS) is practically insoluble in water, pH 1-9 buffers, and in simulated physiological media (pH 1, 5, 5 and 6.5). The synthetic scheme and sufficient characterization data support the structure of the final DS.

During clinical development, the DS was manufactured at (b) (4) (nonclinical and clinical Phases 1 to 3). Subsequently, the DS manufacturing processes were transferred to (b) (4) for commercial manufacture. Three DS batches were manufactured by (b) (4) using process (b) (4), which is representative of the (b) (4) commercial process (b) (4). Three DS batches were also manufactured by (b) (4) for registration, stability and validation purposes. There were minor differences between the (b) (4) and (b) (4) processes; but these differences did not impact the quality of the intermediates and final DS. The comparability results for the (b) (4) and (b) (4) batches, including impurity profile and available stability data, demonstrate that the drug substance from both sites are comparable.

The drug substance specification includes controls on polymorph and particle size. Sufficient risk assessment for mutagenic and elemental impurities is provided. There are no impurities above the qualification threshold in the specification.

Based on the DS stability data for the three validation/stability batches (b) (4)

(b) (4), a re-test date of (b) (4) has been established. This NDA is recommended for approval from a drug substance perspective.

For additional details, refer to the drug substance review by Sharon Kelly.

Drug Product:

Pretomanid Tablet, 200 mg, is a white to off-white, oval shaped, uncoated immediate release tablet for oral use. The tablet is debossed with M on one side and P200 on the other side. Common compendial excipients for solid oral dosage forms are used in the formulation. All inactive ingredients are within the allowable Inactive Ingredients (IIG) database limits for an oral solid dosage form. The product is packaged in either a unit dose blister pack, or 60 cc HDPE child-resistant bottle containing 30 tablets.

In the drug product specification, all specified impurities are controlled at NMT (b) (4)%. Since the maximum daily dose is 200 mg, (b) (4). In the original submission, the applicant did not include the limit for (b) (4). Upon request, the applicant included (b) (4)

The registration stability data at 30 °C/75% RH for 12 months indicate that the drug product shows little or no sign of degradation in both proposed container closure systems of blister packs and HDPE bottles. Based on the data provided, the shelf life for pretomanid tablets can be granted as follows:

- Blister packs: 18 months when stored below 30°C (86°F).
- HDPE bottles: 24 months when stored below 30°C (86°F)

For additional details refer to the drug product review by Yong Wang.

Addendum to Drug Product Review:

The drug product review described one pending IR, copied below.

Update the drug product regulatory specification to reflect the revised limit of NMT (b) (4) in section 3.2.P.8.1.2 (Stability Specification).

The applicant responded to this IR on 04/23/2019 and the stability specification table (section 3.2.P.8.1, table 2) was updated to list the acceptance criteria for (b) (4). This response is acceptable.

The drug product review captured that the HDPE bottle is child resistant, but there was no statement regarding if the blister pack was child-resistant. The following IR was sent on 5/3/2019:

Section 3.2.P.7 describes that the HDPE bottle is child resistant, but does not describe if the blister pack is child resistant. Please confirm if the blister pack is child resistant. Refer to 16 CFR 1600.

The applicant responded on 5/7/2019 that the blister pack is also child resistant. This response is acceptable.

This NDA is recommended for approval from the Drug Product perspective.

Process and Facilities:

The manufacture of pretomanid tablets use the following unit operations: (b) (4)

(b) (4)

Following a review of the application, and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 212862 are found to be acceptable. No preapproval inspections were requested during this review cycle.

For additional details, refer to the process and facilities review by Aditi Thakur.

Biopharmaceutics:

The Biopharmaceutics Review evaluated **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, and **3)** the data supporting the bridge between different drug substance and drug product manufacturing sites and manufacturing processes throughout the drug product development. This included the comparison of the drug product batches from Mylan, (b) (4), and (b) (4). The composition of the drug product manufactured at (b) (4) and (b) (4) is the same as the composition of the drug product manufactured at Mylan Laboratories Ltd., India. However, different equipment and manufacturing processes were used for manufacturing the drug product at (b) (4) and Mylan Laboratories Ltd.

The dissolution method was found acceptable and a dissolution acceptance criterion of “Q= (b) (4)% in 30 minutes” was recommended for the drug product. The Applicant provided in vitro dissolution data in multi-pH dissolution media for three registration

batches of the commercial drug product manufactured at Mylan Laboratories Limited, containing drug substance manufactured at (b) (4). The applicant also provided dissolution data for the clinical batches manufactured at (b) (4) (b) (4) and (b) (4), to bridge the drug product batches dosed in the pivotal Phase 3 clinical study (NiX-TB) to the proposed commercial drug product. The dissolution profile data for the bio-batches manufactured at (b) (4) and (b) (4) in acetate buffer, pH 4.5 and phosphate buffer, pH 6.8 are similar to the three registration batches manufactured at Mylan Laboratories.

From the Biopharmaceutics perspective, NDA 212862 for Pretomanid Tablets, 200 mg is recommended for approval.

For additional details, refer to the review by Parnali Chatterjee.

Environmental Assessment:

21 CFR 21.31(a) referenced for categorical exclusion. Dr. Raanan Bloom communicated via e mail on 1/14/2019 that if approved, this product would be expected to introduce low levels of the API into the environment, and that significant environmental impacts are not expected. For further details, refer to the drug product review by Yong Wang.

C. Special Product Quality Labeling Recommendations (NDA only)

The comments from the labeling review were communicated to the OND PM.

D. Final Risk Assessment (see Attachment)



Erika
Englund

Digitally signed by Erika Englund

Date: 5/10/2019 11:45:58AM

GUID: 51389ea30003450414230afb8c3e8114



BIOPHARMACEUTICS

NDA: 212862

Drug Product Name / Strength: Pretomanid (PA-824) Tablets, 200 mg

Route of Administration: Oral

Applicant Name: Global Alliance for TB Drug Development, Inc. (TB Alliance)

Primary Reviewer: Parnali Chatterjee, Ph.D.

Secondary Reviewer: Elsbeth Chikhale, Ph.D.

Background:

The Applicant is seeking approval for immediate-release Pretomanid (PA-824) Tablets, 200 mg to be administered for the treatment of extensively drug resistant (XDR), (b) (4) (b) (4) or treatment intolerant/non-responsive multi-drug resistant (MDR) pulmonary tuberculosis (TB) *via* the 505 (b)(1) regulatory pathway. The recommended daily dose is a single oral dose of pretomanid (PA-824) tablets, 200 mg to be administered once daily for 26 weeks with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg three times per week [with at least 48 hours between doses]) and linezolid (1200 mg daily for up to 26 weeks with dose adjustments for known linezolid toxicities).

Pretomanid Tablets, 200 mg received priority review and Qualified Infectious Disease Product (QIDP) designation. The basis for this submission is a pivotal Phase 3 randomized, open-label, clinical safety and efficacy study (NiX-TB) conducted with bedaquiline, pretomanid, and linezolid in subjects with pulmonary infection of extensively drug resistant tuberculosis (XDR-TB) or treatment intolerant/non-responsive multi-drug resistant tuberculosis (MDR-TB). In total, 109 subjects were dosed with pretomanid (PA-824) tablets, 200 mg in the NiX-TB study. Subjects 1-45 were dosed with drug product bulk batch 13F079 manufactured at (b) (4) (b) (4) with drug substance sourced from (b) (4) (b) (4). On the other hand, subjects 46-109 were dosed with drug product bulk batch ET16004 manufactured at (b) (4) (b) (4) with drug substance sourced from (b) (4) (b) (4). Clinical Good Manufacturing Practice (cGMP) issues were identified at the (b) (4) (b) (4) drug substance manufacturing site. Therefore, the to-be-marketed (TBM) commercial drug substance (b) (4) (b) (4) manufacturing was transferred to (b) (4) (b) (4).

The Applicant provided in vitro dissolution data in multi-pH dissolution media for three registration batches of the TBM commercial drug product manufactured at Mylan Laboratories Limited, containing drug substance manufactured at (b) (4) (b) (4) and dissolution data for the clinical batches, to bridge the drug product batches dosed in the pivotal Phase 3 clinical study (NiX-TB) to the TBM drug product.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated 1) the proposed dissolution method, 2) the proposed dissolution acceptance criterion, and 3) the data supporting the bridge between different drug substance and drug product manufacturing sites and manufacturing processes throughout the drug product development.

Based on the review of the provided information/data, Biopharmaceutics has the following recommendations:

➤ **Dissolution Method:**

The proposed dissolution method was found to be **ACCEPTABLE** for batch release and stability testing of the proposed product based on the dissolution profile data for the various testing parameters, and dissolution data that supports some discriminating ability of the proposed dissolution method.

Parameters	ACCEPTABLE Dissolution Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/ 75 rpm
<i>Media/Volume</i>	0.1 N HCl with 0.5% HDTMA/ 1000 mL
<i>Bath temperature</i>	37.0±0.5 C

➤ **Dissolution Acceptance Criterion:**

The Applicant proposed ‘ $Q = \frac{(b)}{(4)}\%$ in $(b)_{(4)}$ minutes’ and ‘ $Q = \frac{(b)}{(4)}\%$ in $(b)_{(4)}$ minutes’ as the acceptance criteria at batch release and on stability for Pretomanid tablets, 200 mg. However, the dissolution profile data for the registration batches, batches used in clinical studies, and for batches on stability support a dissolution acceptance criterion of ‘ $Q = \frac{(b)}{(4)}\%$ in 30 minutes’ for release and stability testing of the proposed product. In response to an Information Request comment, the Applicant agreed to the recommended one point dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes.

➤ **Bridging:**

- *Bridging due to equipment, manufacturing site, and manufacturing process changes:*

The drug product dosed in the pivotal Phase 3 clinical study, NiX-TB, were manufactured at $(b)_{(4)}$ as well as at $(b)_{(4)}$. Because, cGMP issues were identified at the $(b)_{(4)}$ drug substance manufacturing site $(b)_{(4)}$ the manufacturing process for the drug substance $(b)_{(4)}$ was transferred to $(b)_{(4)}$. The composition of the drug product manufactured at $(b)_{(4)}$ and $(b)_{(4)}$ is the same as the composition of the drug product manufactured at Mylan Laboratories Ltd., India. However, different equipment and manufacturing processes were used for manufacturing the drug product at $(b)_{(4)}$ and Mylan Laboratories Ltd.

The Applicant provided adequate dissolution profile data using the proposed dissolution method and in multi-pH dissolution media (acetate buffer, pH 4.5 and phosphate buffer, pH 6.8) for the batches manufactured at $(b)_{(4)}$ and $(b)_{(4)}$ and dosed in the pivotal Phase 3 clinical study, Nix-TB to provide a ‘bridge’ to the drug product manufactured at the proposed commercial manufacturing site, Mylan Laboratories Ltd., India.



➤ ***Biopharmaceutics Risk Assessment:***

The drug substance exhibits low aqueous solubility, and the proposed drug product is developed as an immediate-release product. The Applicant provided dissolution data to demonstrate that the dissolution profiles of the different batches manufactured at different sites with different equipment and manufacturing processes are similar. Based on the overall dissolution data at batch release and on stability, from a Biopharmaceutics perspective, the risk of dissolution failure during batch release and stability testing is low.

➤ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 212862 for Pretomanid Tablets containing 200 mg of pretomanid (PA-824) is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

➤ **LIST OF SUBMISSIONS REVIEWED:**

Submissions Reviewed	Reference ID
IND 69580 Meeting Minutes	Dated 05/30/2018 (https://dartrts.fda.gov/dartrts/ViewDocument?documentId=090140af8049bb20)
Original NDA Submission 212862	Dated 12/14/2018, SDN 1 (\\cdsesub1\evsprod\nda212862\0001\m2\27-clin-sum\summary-biopharm.pdf)
Response to Information Request Comment #1	Dated 03/13/2019, SDN 10 (\\cdsesub1\evsprod\nda212862\0011\m1\us\111-information-amendment\response-to-fdas-nda-cmc-ir.pdf)
Response to Information Request Comment #2	Dated 03/20/2019, SDN 12 (\\cdsesub1\evsprod\nda212862\0012\m1\us\111-information-amendment\response-to-fda-nda-cmc-ir.pdf)

➤ **DRUG PRODUCT:**

The to-be-marketed (TBM) 200 mg strength drug product is a white to off-white oval shaped, immediate-release, uncoated tablet, debossed with M on one side and P200 on the other side, containing 200 mg pretomanid. The TBM drug product is manufactured by (b) (4)

The composition of the 200 mg proposed TBM drug product is provided in **Table 1**.

Table 1. Composition of Pretomanid Tablets containing 200 mg of pretomanid

Ingredient/Pharmacopeial standard	Function	%w/w	Weight per Unit (mg)
Pretomanid	Active	(b) (4)	200.0
Lactose Monohydrate, NF			(b) (4)
Microcrystalline Cellulose, NF			
Sodium Starch Glycolate (b) (4), NF			
Magnesium Stearate, NF			
Colloidal Silicon Dioxide, NF			
Sodium Lauryl Sulfate, USP			
Povidone, USP (b) (4)			
Total		100%	800.0 mg

NF = National Formulary; USP = United States Pharmacopeia

➤ **MANUFACTURING SITES FOR THE PROPOSED DRUG PRODUCT:**

The Applicant identified the following manufacturing sites for Pretomanid Tablets, 200 mg used in the Phase 1, Phase 2, and Phase 3 clinical studies, and for the registration batches (see **Table 2**).

Table 2. Manufacturing sites for Pretomanid Tablets, 200 mg used in the Phase 1, Phase 2, and Phase 3 clinical studies, and the registration batches

Drug Product Manufacturing Site	Activities	Batch Number	Date Manufactured
(b) (4)	Formulation development, manufacture of Phase 1, Phase 2a/b, and Phase 3 clinical supply of Pretomanid Tablets, 200 mg	11C014 (Clinical)	March 2011
		13F079 (Pivotal Clinical)	June 2013
	Additional manufacture of Phase 2c and Phase 3 clinical supply of Pretomanid Tablets, 200 mg	ET14067 ET16004 (Pivotal Clinical)	July 2014 January 2016
Mylan Laboratories Limited (Ltd), Aurangabad, India	Manufacture of three registration batches and proposed commercial manufacturing site	2014678	February 2018
		2014679	
		2014680	

The drug product dosed in subjects 1 through 45 in the pivotal Phase 3 clinical study, NiX-TB was manufactured at (b) (4). However, subjects 46-109 enrolled in the pivotal Phase 3 study, Nix-TB were dosed with drug product manufactured at (b) (4). The FDA noted cGMP issues at the (b) (4) drug substance manufacturing site (b) (4). Therefore, the manufacturing process of the drug substance (b) (4) was transferred to (b) (4). The batch numbers for the drug product batches manufactured at (b) (4) and (b) (4) and dosed in the pivotal Phase 3 clinical study, Nix-TB are provided in **Table 2**, along with the registration batches that were not used in any clinical study.

The composition of the drug product manufactured at (b) (4) and (b) (4) are the same as the composition of the drug product manufactured at Mylan Laboratories Ltd., India. However, the manufacturing process for the drug product manufactured at both (b) (4) and Mylan Laboratories Ltd includes (b) (4) which was not used in the manufacturing process at (b) (4). The Applicant provided dissolution profile data for the batches manufactured at (b) (4) and (b) (4) and dosed in the pivotal Phase 3 clinical study, Nix-TB to provide a ‘bridge’ to the drug product manufactured at Mylan Laboratories Ltd., India. The assesment of the dissolution profile data to ‘bridge’ the drug

product manufactured at (b) (4) and (b) (4) used in the clinical trials to the TBM drug product manufactured at Mylan Laboratories Ltd., India will be discussed under “*Bridging*”.

➤ **BCS DESIGNATION**

An official BCS designation for the proposed drug product was not requested, nor required. The active ingredient in the proposed drug product is a new molecular entity (NME), pretomanid (molecular formula C₁₄H₁₂F₃N₃O₅; molecular weight 359.26 grams/mole), a white to off-white crystalline drug substance with a chiral center (6*S*). The *S*-isomer is the enantiomeric form of the drug substance in the drug product. The drug substance exhibits four solid-state forms; three crystalline forms (two polymorphic (b) (4) and one solvated form) and an amorphous form. (b) (4) is the most thermodynamically stable solid-state form of the drug substance in the drug product (b) (4).

- **Solubility:**

The solubility profile of pretomanid was determined in buffer solutions across the physiological pH range 1.2-6.5 at 37 C (see **Table 3a** and **Table 3b**).

Reviewer’s Assessment of Drug Substance Solubility:

As shown in **Table 3a** and **Table 3b**, pretomanid exhibits a pH-independent solubility profile in buffer solutions across the physiological pH range 1.2-6.5 at 37 C. The highest solubility of pretomanid is in simulated physiological media, pH 5.0 (~87 µg/mL or 0.087 mg/mL). The highest dose of pretomanid i.e., 200 mg will not be soluble in 250 mL buffer solution across the physiological pH range 1.2-6.8 at 37 C. Consequently, pretomanid can be categorized as a ‘low’ soluble drug substance.

Table 3a. Solubility of pretomanid drug substance in buffer solutions across the physiological pH range 1.0-4.0 at 37 C

Buffer		Solubility (mg/mL)	Average Solubility (mg/mL)	Parts of solvent required for 1 part of solute	Solubility
pH 1.0	Prep-1	0.016	0.016	62,500	Practically insoluble
	Prep-2	0.016			
	Prep-3	0.015			
pH 2.0	Prep-1	0.012	0.012	83,333	Practically insoluble
	Prep-2	0.013			
	Prep-3	0.013			
pH 3.0	Prep-1	0.015	0.015	66,666	Practically insoluble
	Prep-2	0.014			
	Prep-3	0.015			
pH 4.0	Prep-1	0.014	0.013	76,923	Practically insoluble
	Prep-2	0.013			
	Prep-3	0.012			

Table 3b. Solubility of pretomanid drug substance in buffer solutions across the physiological pH range 1.5-6.5 at 37 C

Buffer		Solubility (mg/mL)	Average Solubility (mg/mL)	Parts of solvent required for 1 part of solute	Solubility
pH 6.0	Prep-1	0.011	0.010	100,000	Practically insoluble
	Prep-2	0.010			
	Prep-3	0.010			
pH 7.0	Prep-1	0.010	0.010	100,000	Practically insoluble
	Prep-2	0.010			
	Prep-3	0.010			
pH 8.0	Prep-1	0.015	0.015	66,666	Practically insoluble
	Prep-2	0.014			
	Prep-3	0.015			
pH 9.0	Prep-1	0.014	0.014	71,428	Practically insoluble
	Prep-2	0.014			
	Prep-3	0.013			
Biological media pH 1.5	Prep-1	0.014	0.014	71,428	Practically insoluble
	Prep-2	0.014			
	Prep-3	0.014			
Biological media	Prep-1	0.085	0.087	11,494	Practically insoluble
	Prep-2	0.086			
pH 5.0	Prep-3	0.088			
Biological media pH 6.5	Prep-1	0.027	0.027	37,037	Practically insoluble
	Prep-2	0.027			
	Prep-3	0.026			

- **Permeability/Absorption:**

Based on the single-dose, two-treatment, two-period, two-sequence, open-label, cross-over, food effect study CL-009, exposure to pretomanid was found to be substantially higher (~2 fold) in the presence of food (AUC~53.0 $\mu\text{g}\cdot\text{hr}/\text{mL}$) as compared to the fasted state (AUC~28.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$) following a 200 mg dose (see **Table 4b**), and did not exhibit dose-linearity over a 50 mg to 200 mg dose range (see **Table 4a** and **Table 4b**). The time-to-maximum concentration (T_{max}) was achieved in 4.00 hours under fasted condition suggesting a slower absorption profile of the drug and occurred 1-1.5 hours later in the presence of food at a 200 mg dose (see **Table 4b**). Exposure to pretomanid and T_{max} was found to be higher in women as compared to men at a 200 mg dose (see **Table 4b**). Furthermore, pretomanid demonstrated a long elimination half-life ($t_{1/2}$) of ~17 hours that was independent of food effect.

Reviewer's Assessment of Permeability/Absorption:

Based on the food effect study, CL-009, it can be concluded that pretomanid exhibits a saturable and moderate-high permeability profile.

Table 4a . Pharmacokinetic parameters following 50 mg single-dose, food effect study, CL-009 for Pretomanid Tablets (Batch # 7H112 manufactured at (b) (4))

Dose	Parameters	Fed Mean ± SD			Fasted Mean ± SD		
		OVERALL (N = 16)	MALE (N = 8)	FEMALE (N = 8)	OVERALL (N = 16)	MALE (N = 8)	FEMALE (N = 8)
50 mg	C_{max} (µg/mL)	0.541 ± 0.056	0.531 ± 0.077	0.550 ± 0.023	0.392 ± 0.084	0.355 ± 0.082	0.429 ± 0.073
	t_{max} (hr)[1]	4.00 (2.00, 8.01)	4.00 (3.00, 6.00)	4.00 (2.00, 8.01)	4.00 (2.00, 8.00)	4.00 (2.00, 8.00)	3.00 (2.00, 4.00)
	$t_{1/2}$ (hr)	19.2 ± 3.76	19.4 ± 4.39	19.1 ± 3.29	18.9 ± 4.41	19.0 ± 5.23	18.8 ± 3.78
	AUC_{∞} (µg*hr/mL)	14.7 ± 3.1	14.5 ± 3.5	14.9 ± 3.0	10.4 ± 3.4	10.4 ± 4.6	10.3 ± 1.9
	CL/F (L/hr)	3.56 ± 0.778	3.64 ± 0.894	3.49 ± 0.697	5.30 ± 1.73	5.59 ± 2.31	5.01 ± 0.916
	Vd/F(L)	95.8 ± 12.0	97.2 ± 8.68	94.4 ± 15.1	136 ± 23.0	139 ± 27.3	133 ± 19.1

AUC_{∞} = area under the drug concentration-time curve from zero to infinity; CL/F = oral clearance;

C_{max} = maximum plasma concentration; hr = hour; SD = standard deviation; $t_{1/2}$ = half-life; t_{max} = time of occurrence for maximum (peak) drug concentration; V_d/F = apparent volume of distribution following oral administration

[1] t_{max} is presented as median (minimum, maximum).

Source: CL-009 Table 11.1

Table 4b . Pharmacokinetic parameters following 200 mg single-dose, food effect study, CL-009 for Pretomanid Tablets (Batch #7H112 manufactured at (b) (4))

Dose	Parameters	Fed Mean ± SD			Fasted Mean ± SD		
		OVERALL (N = 16)	MALE (N = 8)	FEMALE (N = 8)	OVERALL (N = 16)	MALE (N = 8)	FEMALE (N = 8)
200 mg	C_{max} (µg/mL)	1.97 ± 0.30	1.80 ± 0.23	2.13 ± 0.27	1.13 ± 0.21	1.06 ± 0.23	1.19 ± 0.20
	t_{max} (hr) [1]	5.00 (3.00, 8.07)	6.00 (3.00, 8.00)	4.00 (3.00, 8.07)	4.00 (2.00, 6.00)	4.00 (4.00, 6.00)	3.50 (2.00, 6.00)
	$t_{1/2}$ (hr)	17.4 ± 2.76	16.7 ± 2.24	18.2 ± 3.17	16.9 ± 3.08	16.4 ± 2.83	17.3 ± 3.45
	AUC_{∞} (µg*hr/mL)	53.0 ± 10.6	48.8 ± 9.1	57.1 ± 11.0	28.8 ± 8.3	27.5 ± 8.4	30.0 ± 8.5
	CL/F (L/hr)	3.92 ± 0.764	4.22 ± 0.767	3.61 ± 0.672	7.55 ± 2.47	8.09 ± 3.21	7.01 ± 1.46
	Vd/F(L)	97.0 ± 17.2	101 ± 18.9	93.2 ± 15.7	180 ± 51.3	187 ± 61.0	174 ± 42.7

Particle Size Distribution:

Because pretomanid exhibits low solubility in buffer solutions across the physiological pH range, particle size (PS) of the drug substance can alter the dissolution profile and bioavailability (BA) of the drug product.

The Applicant proposed $D_{90}^{(b) (4)}$ μm as the particle size distribution (PSD) acceptance criterion for the drug substance based on the dissolution data for drug products manufactured at $(b) (4)$ and $(b) (4)$, using different PSD (see **Table 5a** and **Table 5b**).

Table 5a. Drug products manufactured with varying particle size distribution (PSD) of the drug substance

Batch number	PA8-200-F-002 (Control)	PA8-200-F-011 ($(b) (4)$) API	PA8-200-F-012 ($(b) (4)$) API
Details of API - PSD	$(b) (4)$		
API Manufacturer	$(b) (4)$		
API batch No.	AFKH001863 (A.R. No. 40000997829)	27083789	27083617

Table 5a shows that drug product batch PA8-200-F-002 was manufactured at $(b) (4)$ with drug substance batch AFKH001863. Two other drug product batches were manufactured at the $(b) (4)$, PA8-200-F-011, with drug substance batch 27083789 (registration batch) and PA8-200-F-012, with drug substance batch 27083617.

The dissolution data for the three batches is provided in **Table 5b**.

Table 5b. Mean in vitro dissolution profile data for drug product batches manufactured with varying particle size distribution (PSD) of the drug substance

Batch No.	PA8-200-F-002 (Control)	PA8-200-F-011 (b) (4) API	PA8-200-F-012 (b) (4) API
(b) (4)			

The dissolution profile data for batch, PA8-200-F-011, manufactured at (b) (4) with (b) (4) (b) (4) as compared to the batch, PA8-200-F-012, manufactured at (b) (4) and drug product batch PA8-200-F-002 manufactured at (b) (4)

However, the difference in dissolution between batches with different particle size is not significant (<10%), therefore, the Applicant (b) (4) the drug substance and proposed D₉₀ (b) (4) μm as the PSD for the drug substance in the drug product. A bioavailability (BA) study, CL-009 (see **Table 4a** and **Table 4b**) was conducted with the drug product containing (b) (4) drug substance with D₉₀ (b) (4) μm. The adequacy of the BA study will be assessed by the OCP reviewers.

Reviewer’s Assessment of proposed PSD acceptance criterion:

Changes to the PSD between D₉₀ of (b) (4) and (b) (4) μm do not exhibit significant changes in the dissolution profiles. This can indicate that the in vitro dissolution method is not sensitive to changes in PSD, but it has an effect in vivo; or the PSD does not effect the dissolution in vitro and in vivo. Therefore, the drug substance Reviewer should set the PSD acceptance criteria based on the clinical batches.

➤ **DISSOLUTION INFORMATION:**

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product and is utilized **1)** as a quality control tool during the product development process, **2)** for bridging between batches used in the pivotal clinical study (NiX-TB) and the commercial manufacturing site, **3)** for batches on stability, and **4)** (b) (4)

➤ **DISSOLUTION METHOD:**

The proposed dissolution method (see in **Table 6a**) was found to exhibit some discriminating power and is **ACCEPTABLE** for routine quality control testing of the proposed drug product based on the Applicant's Dissolution Method Development Report provided in the NDA.

Table 6a. ACCEPTABLE dissolution method for Pretomanid Tablets, 200 mg

Parameters	Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Medium/Volume</i>	0.1 N HCl with 0.5% HDTMA/1000 mL
<i>Bath temperature</i>	37.0±0.5 C

Dissolution Method Development Report (Protocol No. CPS-F-Pa8-P/17003) for Pretomanid Tablets, 200 mg:

(b) (4)

(b) (4)



Overall Reviewer’s Assessment of the Proposed Dissolution Method:

The Applicant provided dissolution profile data that supports the proposed dissolution method: USP Apparatus 2 at 75 rpm paddle speed in 0.1N HCl containing 0.5% w/v HDTMA at 37°C. Based on the totality of the dissolution data, the proposed dissolution method exhibits discriminatory ability to differentiate drug product batches that are manufactured (b) (4)

The proposed dissolution method is acceptable as a quality control tool for dissolution testing of the proposed drug product.

➤ ***PROPOSED DISSOLUTION ACCEPTANCE CRITERION:***

The Applicant proposed “ $Q = \frac{(b)}{(4)}\%$ in $(b) (4)$ minutes’ and ‘ $Q = \frac{(b)}{(4)}\%$ in $(b) (4)$ minutes” as the dissolution acceptance criterion for batch release and stability testing of the 200 mg strength proposed drug product.

Dissolution Data at Drug Product Batch Release:

The dissolution profile data for drug product batches, 11C014 and 13F079 (dosed in the pivotal clinical trial NiX-TB) manufactured at (b) (4), batches ET14067 and ET16004 (dosed in the pivotal clinical trial NiX-TB) manufactured at (b) (4), and three registration batches, 2014678, 2014679, and 2014680, manufactured in Mylan and not used in any clinical study, using the proposed dissolution method are provided in **Figure 3a** and **Figure 3b**.

Figure 3a. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at (b) (4) and Mylan Laboratories Ltd., India using the proposed dissolution method

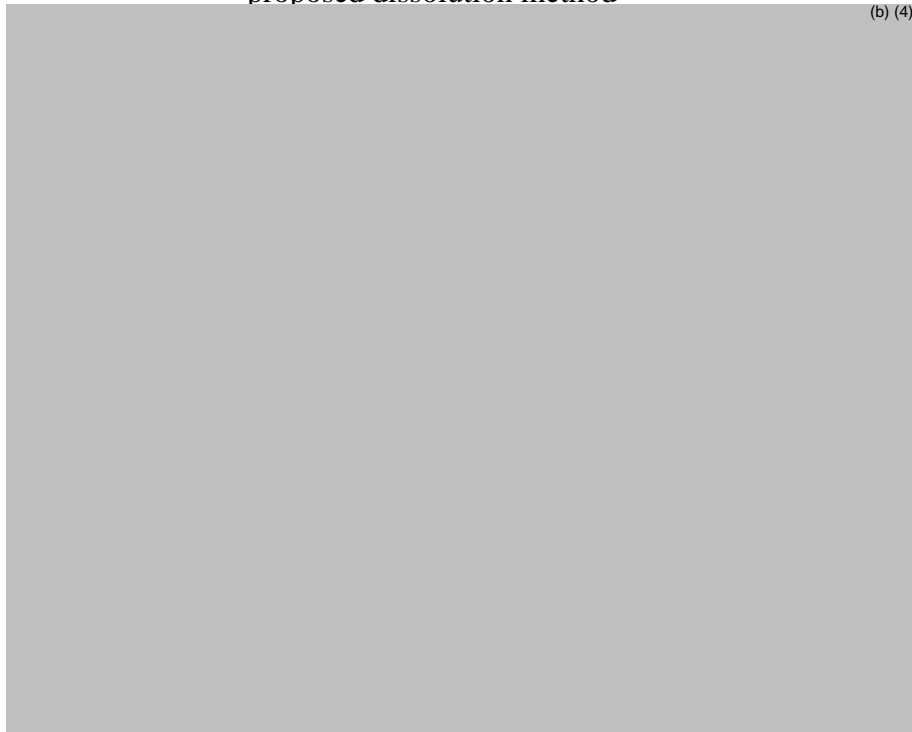
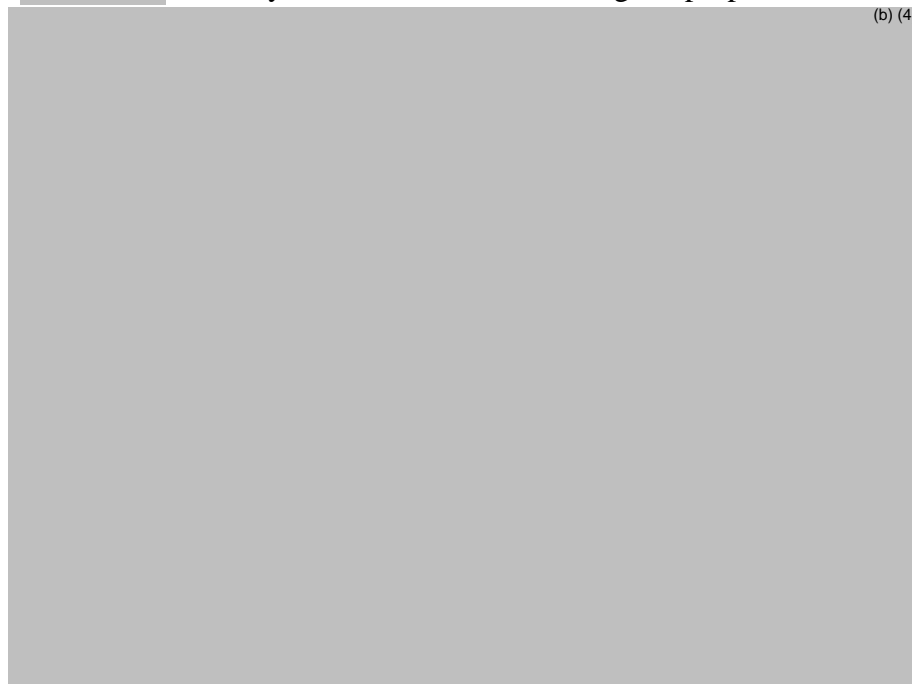


Figure 3b. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at (b) (4) and Mylan Laboratories Ltd. using the proposed dissolution method



The dissolution profile data for the batches manufactured at (b) (4) and Mylan Laboratories Ltd., India are similar, with f_2 value >50 and exhibit (b) (4)% release of pretomanid in 30 minutes (see **Table 7a** and **Table 7b** for f_2 values). Though, the dissolution profile data for the bio-batch 13F079 manufactured at (b) (4) appears to be different in **Figure 3a**, the f_2 value (calculated by this Reviewer) is 54.35 (see **Table 7a**), indicating that the profiles are similar.

Table 7a. Similarity factor ' f_2 ' value for dissolution profile data for the registration batches 2014678, 2014679, and 2014680 manufactured at Mylan Laboratories Ltd and batches 11C014 and 13F079 (dosed in the pivotal clinical trial NiX-TB) manufactured at (b) (4)

Name	F2-Value
Mylan Batch_2014678 Vs Mylan Batch_2014679	68.36
Mylan Batch_2014678 Vs Mylan Batch_2014680	76.86
Mylan Batch_2014678 Vs (b) (4) Batch_11C014	89.16
Mylan Batch_2014678 Vs (b) (4) Batch_13F019	54.35
Mylan Batch_2014679 Vs Mylan Batch_2014680	75.48
Mylan Batch_2014679 Vs (b) (4) Batch_11C014	73.97
Mylan Batch_2014679 Vs (b) (4) Batch_13F019	67.55
Mylan Batch_2014680 Vs (b) (4) Batch_11C014	86.18
Mylan Batch_2014680 Vs (b) (4) Batch_13F019	61.22
(b) (4) Batch_11C014 Vs (b) (4) Batch_13F019	57.81

Table 7b. Similarity factor ' f_2 ' value for dissolution profile data for for the registration batches 2014678, 2014679, and 2014680 manufactured at Mylan Laboratories Ltd and batches ET14067 and ET16004 (dosed in the pivotal clinical trial NiX-TB) manufactured at (b) (4)

Name	F2-Value
Mylan Batch_2014678 Vs Mylan Batch_2014679	71.92
Mylan Batch_2014678 Vs Mylan Batch_2014680	77.04
Mylan Batch_2014678 Vs (b) (4) Batch_ET14067	68.38
Mylan Batch_2014678 Vs (b) (4) Batch_ET16004	69.56
Mylan Batch_2014679 Vs Mylan Batch_2014680	89.75
Mylan Batch_2014679 Vs (b) (4) Batch_ET14067	86.09
Mylan Batch_2014679 Vs (b) (4) Batch_ET16004	59.10
Mylan Batch_2014680 Vs (b) (4) Batch_ET14067	77.98
Mylan Batch_2014680 Vs (b) (4) Batch_ET16004	64.94
(b) (4) Batch_ET14067 Vs (b) (4) Batch_ET16004	56.20

Dissolution Data at Long-Term and Accelerated Stability Testing:

The dissolution profile data for three registration batches in blister packs and HDPE bottles manufactured at Mylan Laboratories Ltd. on long-term and accelerated stability conditions for 6 months indicate $\text{ }^{(b)}(4)\%$ release of pretomanid in 30 minutes. No significant trend in the dissolution profile data is observed for batches stored at long-term and accelerated stability conditions (see **Figure 3c** and **Figure 3d**).

Figure 3c. Mean dissolution profile data for registration batch 2014678 of Pretomanid Tablets, 200 mg in blister packs and HDPE bottles manufactured at Mylan Laboratories Ltd., India using the proposed dissolution method stored at long term and accelerated stability condition for 6 months

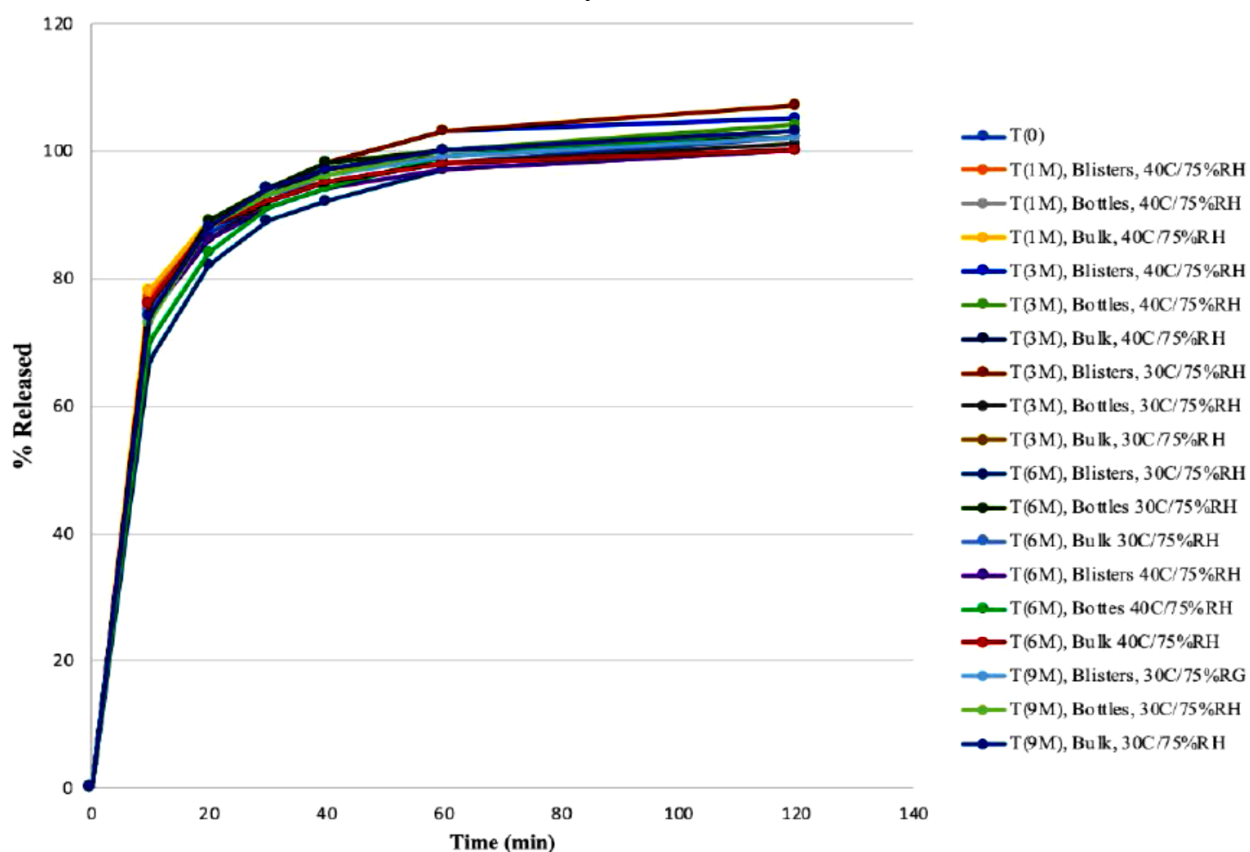
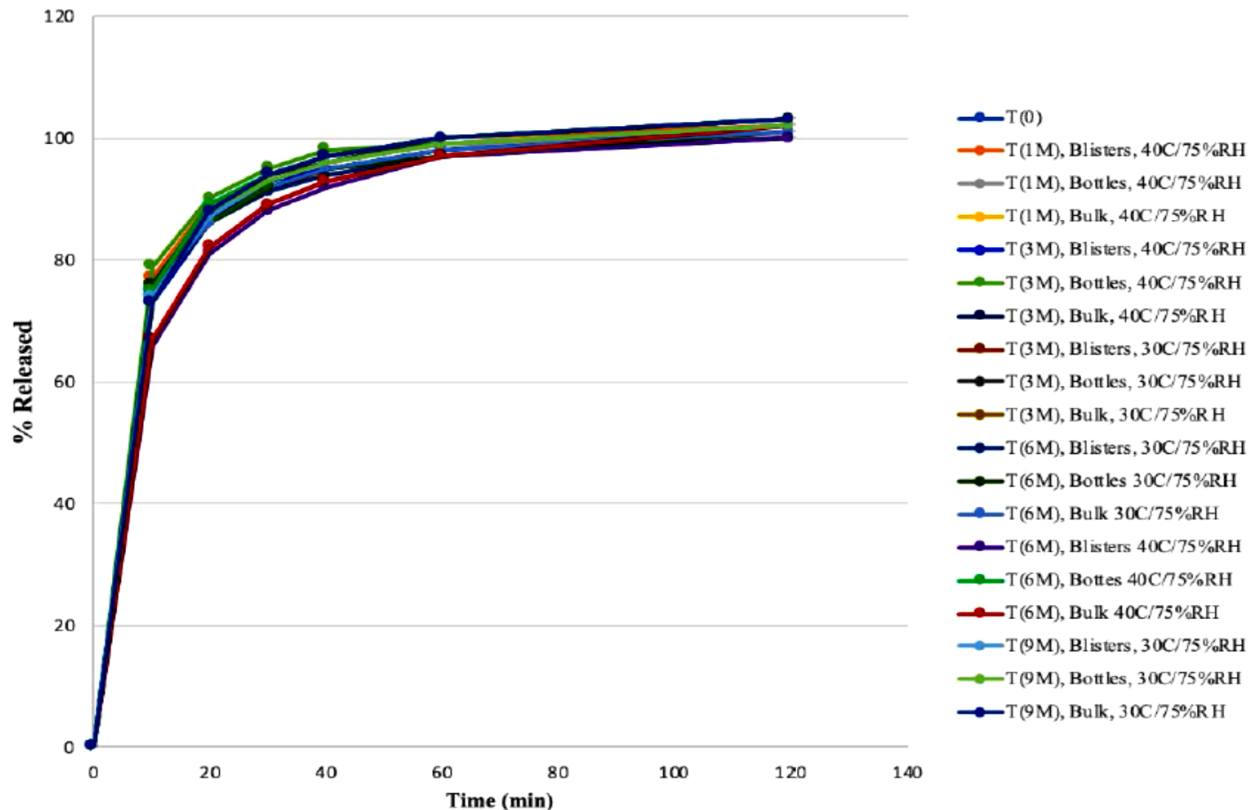


Figure 3d. Mean dissolution profile data for registration batch 2014680 of Pretomanid Tablets, 200 mg in blister packs and HDPE bottles manufactured at Mylan Laboratories Ltd., India using proposed dissolution method stored at long term and accelerated stability condition for 6 months



Reviewer’s Assessment of the Proposed Dissolution Acceptance Criterion:

Based on the totality of the dissolution data, from a Biopharmaceutics perspective, the proposed dissolution acceptance criterion “ $Q = \frac{(b)}{(4)}\%$ in $(b) (4)$ minutes” and “ $Q = \frac{(b)}{(4)}\%$ in $(b) (4)$ minutes” is permissive and not acceptable. The dissolution data support a dissolution acceptance criterion of “ $Q = \frac{(b)}{(4)}\%$ in 30 minutes”. An Information Request comment was conveyed to the Applicant to implement “ $Q = \frac{(b)}{(4)}\%$ in 30 minutes” for batch release and stability testing of the proposed drug product, to which the Applicant agreed.

➤ **Bridging of Equipment, Manufacturing Process, and Manufacturing Site Changes:**

The drug product that was dosed in subjects 1 through 45 in the pivotal Phase 3 clinical study, NiX-TB was manufactured at $(b) (4)$ and contained drug substance from $(b) (4)$. On the other hand, subjects 46-109 enrolled in the pivotal Phase 3 study, Nix-TB were dosed with drug product manufactured at $(b) (4)$, and also contained drug substance from $(b) (4)$. Because, cGMP issues were identified at the $(b) (4)$ drug substance manufacturing site $(b) (4)$

(b) (4), the Applicant transferred the manufacturing process of the drug substance (b) (4)

Bridging of Equipment, Manufacturing Site and Process Changes:

The composition of the drug products manufactured at (b) (4), and Mylan Laboratories Ltd., India is the same. However, the manufacturing process for the drug product manufactured at (b) (4) and Mylan Laboratories Ltd includes (b) (4)



(b) (4) drug product batch 13F079

(b) (4) drug product batch ET16004



(b) (4) drug product batch 13F079

Mylan registration batches 2014678, 2014679, 2014680



(b) (4) drug product batch ET16004

Mylan registration batches 2014678, 2014679, 2014680

The Applicant provided multi pH dissolution profile data for the batches manufactured at (b) (4) and (b) (4) and dosed in the pivotal Phase 3 clinical study, Nix-TB to provide a 'bridge' to the drug product manufactured at Mylan Laboratories Ltd., India, using the proposed the dissolution method (see **Figure 3a** and **Figure 3b**), acetate buffer, pH 4.5 (see **Figure 4a** and **Figure 4b**), and phosphate buffer pH 6.8 (see **Figure 5a** and **Figure 5b**).

Figure 4a. Mean dissolution profile data for pivotal clinical batches of Pretomanid Tablets, 200 mg manufactured at (b) (4) and (b) (4) using acetate buffer, pH 4.5



Figure 4b. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at Mylan Laboratories using acetate buffer, pH 4.5

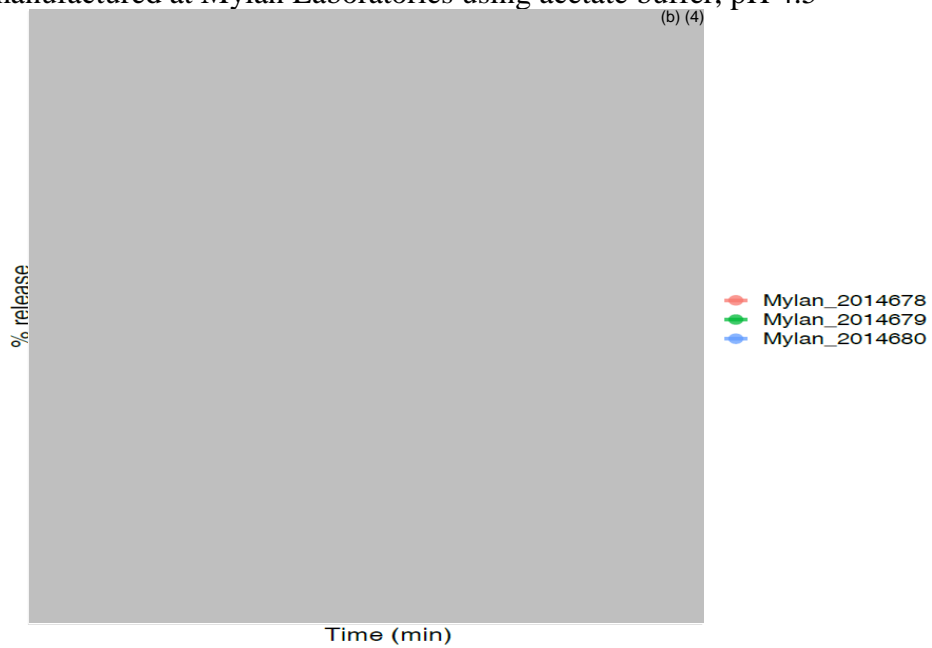


Figure 5a. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at (b) (4) and (b) (4) using phosphate buffer, pH 6.8

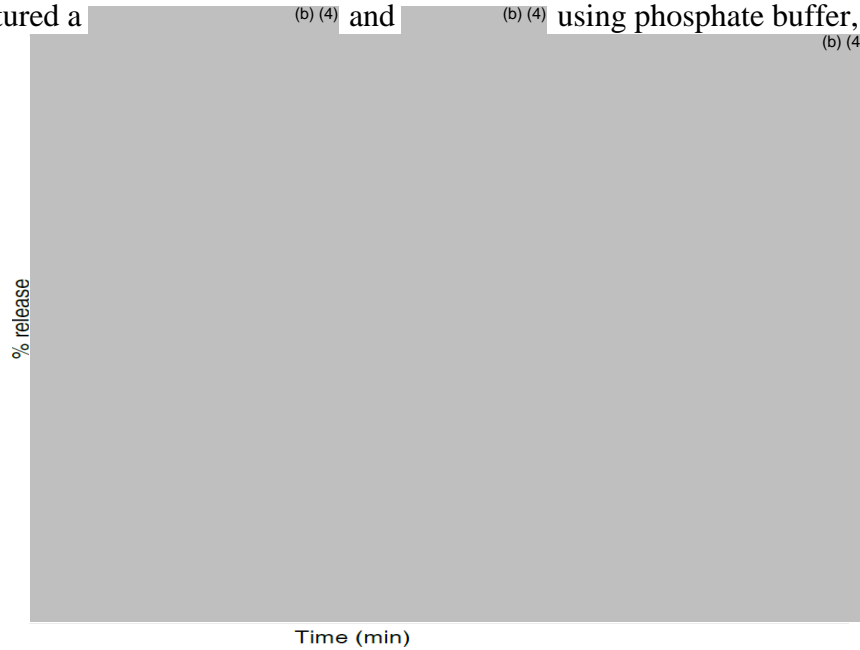


Figure 5b. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at Mylan Laboratories using phosphate buffer, pH 6.8



The dissolution profile data for the bio-batches manufactured at (b) (4) and (b) (4) in acetate buffer, pH 4.5 and phosphate buffer, pH 6.8 are similar to the three registration batches manufactured at Mylan Laboratories, with f_2 value > 50 (calculated by this Reviewer).

Based on the totality of the in vitro dissolution data adequate ‘bridging data’ is provided to bridge the changes in equipment, manufacturing process, and manufacturing site between the commercial TBM drug product and the drug products used in the pivotal Phase III clinical study NiX-TB.

➤ ***BIOPHARMACEUTICS RISK ASSESSMENT:***

Though the drug substance exhibits low solubility profile, the Applicant provided dissolution data to demonstrate that the dissolution profiles of the different batches manufactured at different sites are similar. Based on the overall dissolution data at release and on stability, from a Biopharmaceutics perspective, the risk of dissolution failure during batch release and stability testing is low.

➤ ***POST-APPROVAL COMMITMENTS:*** None

➤ ***LIST OF DEFICIENCIES:*** None

➤ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 212862 for Pretomanid Tablets containing 200 mg of pretomanid (PA-824) is recommended for **APPROVAL**.

APPENDIX I

Table A. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at (b) (4) using the proposed dissolution method

Sample Time Minutes	Batch 11C014				Batch 13F079			
	% Claim Dissolved			% RSD	% Claim Dissolved			% RSD
	Mean	Min	Max		Mean	Min	Max	
5	56	(b) (4)		2.6	50	(b) (4)		10.4
10	75	(b) (4)		1.3	67	(b) (4)		1.9
15	84	(b) (4)		1.0	76	(b) (4)		2.0
20	88	(b) (4)		0.9	81	(b) (4)		2.1
30	94	(b) (4)		1.0	87	(b) (4)		1.8
40	97	(b) (4)		0.9	91	(b) (4)		2.5
45	99	(b) (4)		1.2	93	(b) (4)		2.1
60	101	(b) (4)		1.8	95	(b) (4)		2.1
90	103	(b) (4)		1.3	99	(b) (4)		2.4
120	105	(b) (4)		1.3	100	(b) (4)		2.0

Table B. Mean dissolution profile data for batches of Pretomanid Tablets, 200 mg manufactured at (b) (4) using the proposed dissolution method

Time (min)	DRL			
	Batch ET14067		Batch ET16004	
	%	% RSD	%	% RSD
10	71	0.9	84	1.7
20**	84	0.8	91	0.8
40**	93	0.7	95	0.7
60	97	0.8	97	0.6
120	100	0.8	98	0.7

Table C. Mean dissolution profile data for three registration batches of Pretomanid Tablets, 200 mg manufactured at Mylan Laboratories Ltd., India using the proposed dissolution method

Sample Time Minutes	Batch 2014678				Batch 2014679				Batch 2014680			
	% Claim Dissolved			% RSD	% Claim Dissolved			% RSD	% Claim Dissolved			% RSD
	Mean	Min	Max (b) (4)		Mean	Min	Max (b) (4)		Mean	Minimum	Maximum (b) (4)	
5	56		(b) (4)	3.1	50		(b) (4)	5.8	57		(b) (4)	2.6
10	77		(b) (4)	1.2	72		(b) (4)	3.7	75		(b) (4)	1.2
15	86		(b) (4)	3.1	81		(b) (4)	1.8	82		(b) (4)	0.8
20	89		(b) (4)	1.5	86		(b) (4)	1.4	87		(b) (4)	0.6
30	95		(b) (4)	1.1	92		(b) (4)	0.9	92		(b) (4)	0.5
40	98		(b) (4)	1.0	95		(b) (4)	0.7	95		(b) (4)	0.7
45	100		(b) (4)	1.2	97		(b) (4)	0.9	97		(b) (4)	0.7
60	102		(b) (4)	1.0	98		(b) (4)	0.8	98		(b) (4)	0.7
90	104		(b) (4)	0.8	100		(b) (4)	0.9	100		(b) (4)	0.5
120	105		(b) (4)	0.8	102		(b) (4)	0.8	102		(b) (4)	0.8

Table D. Mean dissolution profile data to highlight the discriminatory ability of the proposed dissolution method for Pretomanid Tablets, 200 mg

Parameter	Dissolution (Percent Label Claim Dissolved after Minutes shown)					
	10	20	40	60	120	Recovery (b) (4)
(b) (4)						
(b) (4)						



Parnali
Chatterjee

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Elsbeth
Chikhale

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LABELING

[IQA Review Guide Reference](#)

NDA 212862

I. Package Insert

1. *Highlights of Prescribing Information*

These highlights do not include all the information needed to use pretomanid safely and effectively. See full prescribing information for pretomanid.

Pretomanid tablets, for oral use

Initial U.S. Approval: XXXX

-----DOSAGE AND ADMINISTRATION-----



(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Proprietary name: N/A Pretomanid tablets
Dosage form, route of administration	Pretomanid tablets, for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 200 mg (3)

2. *Section 2 Dosage and Administration*

2.1 Important Administration Instructions

- 

(b) (4)

- [Redacted]
- [Redacted]

(b) (4)

2.2 Recommended Dosage

[Redacted]

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(12))
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Swallow pretomanid tablets whole with water.

3. Section 3 Dosage Forms and Strengths

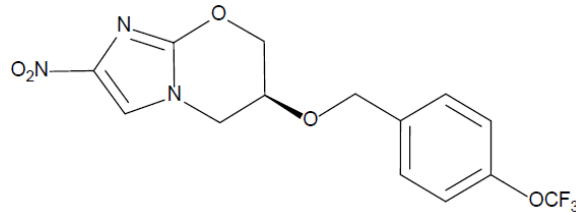
Pretomanid Tablets, 200 mg, are white to off-white oval tablets debossed with M on one side and P200 on the other side.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	Tablets
Strengths: in metric system	200 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pretomanid Tablets, 200 mg, are white to off-white oval tablets debossed with M on one side and P200 on the other side.

4. Section 11 Description

Pretomanid is an oral nitroimidazooxazine antimycobacterial drug.

Pretomanid is a white to off-white to yellow colored powder. The chemical name for pretomanid is (6*S*)-2-Nitro-6-{{4-(trifluoromethoxy)phenyl}methoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine. The molecular formula for pretomanid is C₁₄H₁₂F₃N₃O₅, and the molecular weight is 359.26. The structural formula of pretomanid is as follows:



Each pretomanid tablet contains 200 mg of pretomanid. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulfate, and povidone.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Proprietary name: N/A
Dosage form and route of administration	Oral pretomanid table
Active moiety expression of strength with equivalence statement (if applicable)	N/A
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The inactive ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulfate, and povidone. The following will be communicated to the applicant: <i>List USP/NF names of excipients in alphabetical order (USP <1091>).</i>
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	nitroimidazooxazine antimycobacterial drug
Chemical name, structural formula, molecular weight	Chemical Name: (6S)-2-Nitro-6- {[4-(trifluoromethoxy)phenyl]methoxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine Structural formula: C ₁₄ H ₁₂ F ₃ N ₃ O ₅ Molecular weight: 359.26
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

5. Section 16 How Supplied/Storage and Handling

Pretomanid 200 mg tablets are packaged in either white, round, high-density polyethylene bottles with polypropylene child-resistant closure or child-resistant blister packages comprised of a polyvinylchloride film with foil and paper backing.

Pretomanid 200 mg tablets are white to off-white, oval-shaped tablets debossed with M on one side and P200 on the other side.

NDC Number	Size
49502-476-93	Bottle of 30
49502-476-28	Unit dose blister pack of 28 (2 strips of 14 tablets)

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	Pretomanid 200 mg tablets
Available units (e.g., bottles of 100 tablets)	Bottle of 30 Unit dose blister pack of 28 (2 strips of 14 tablets)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white, oval-shaped tablets debossed with M on one side and P200 on the other side.
Special handling (e.g., protect from light)	(b) (4)
Storage conditions	(b) (4)
	Based on the information provided, the following storage condition is recommended. The recommended statement was discussed in the labeling meeting and agreed upon. <i>Store below 30 °C (86 °F). Dispense only in original container. Keep container tightly closed.</i>
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: The Global Alliance for TB Drug Development (TB Alliance) Manufactured by: Mylan, Laboratories Limited, Hyderabad, 500 096, India

Medication Guide

How should I store

(b) (4)

(b) (4)

Reviewer's Assessment of Package Insert: *Adequate*

With respect of Pharmacological/ therapeutic class, the discussion has been initiated with P/T reviewer. P/T reviewer will make the final decision and the decision will be communicated to the applicant.

The following comments have been discussed in the labeling meeting (4/3/2019) and will be communicated to the applicant.

In section 11 Description, list USP/NF names of excipients in alphabetical order (USP <1091>).

In section 16 How Supplied/Storage and Handling, remove (b) (4) and use the following sentences:

Store below 30 °C (86 °F).

Dispense only in original container. Keep container tightly closed.

In Medication Guide for How should I store (b) (4)

, replace (b) (4) with the following:

Store below 30 °C (86 °F). Dispense only in original container. Keep container tightly closed.

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

➤ *Any deficiencies should be listed at the end in the "List of Deficiencies"*

II. Labels:**1. Container and Carton Labels**

HDPE bottle label:

Item for HDPE bottle	Information provided in the HDPE container label	Information provided in the HDPE carton label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Pretomanid Tablets Adequate	Pretomanid Tablets Adequate
Dosage strength	Each tablet contains: Pretomanid 200mg	Each tablet contains: Pretomanid 200mg
Net contents	30 tablets	30 tablets
“Rx only” displayed prominently on the main panel	“Rx only” is available	“Rx only” is available
NDC number (21 CFR 207.35(b)(3)(i))	NDC 49502-476-93	NDC 49502-476-93
Lot number and expiration date (21 CFR 201.17)	The space for lot numbers and expiration is available Refer to DMEPA’s review for more comments	The space for lot numbers and expiration is available Refer to DMEPA’s review for more comments
Storage conditions	Keep this and all medication out of the reach of children. Store [redacted] (b) (4) [redacted] Dispense only in original container. Keep container tightly closed.	Keep this and all medication out of the reach of children. Store [redacted] (b) (4) [redacted] Dispense only in original container. Keep container tightly closed. The following statement should be communicated to the applicant: <i>In the carton and container labels, replace [redacted] (b) (4) [redacted] with the following condition: “Store below 30 °C (86 °F)”.</i>
Bar code (21CFR 201.25)	Available	Available
Name of manufacturer/distributor	Manufactured by: Mylan Laboratories Limited Hyderabad - 500 096, India Manufactured for: TB Alliance New York, NY 10005	Manufactured by: Mylan Laboratories Limited Hyderabad - 500 096, India Manufactured for: TB Alliance New York, NY 10005

And others, if space is available		N/A

Labels for blister pack

Item for blister packs	Information provided in the blister label	Information provided in the blister carton label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Pretomanid Tablet 200 mg Adequate	Pretomanid Tablets 200 mg Adequate
Dosage strength	Pretomanid Tablet 200mg	Each tablet contains 200 mg of pretomanid
Net contents	N/A (N/A for blister)	28 tablets
“Rx only” displayed prominently on the main panel	“Rx only” is available	“Rx only” is available
NDC number (21 CFR 207.35(b)(3)(i))	N/A Refer to blister carton label	NDC 49502-476-28
Lot number and expiration date (21 CFR 201.17)	The space for lot numbers and expiration is available Refer to DMEPA’s review for more comments	The space for lot numbers and expiration is available Refer to DMEPA’s review for more comments
Storage conditions	Not applicable	Keep this and all medication out of the reach of children. Store (b) (4) The following statement should be communicated to the applicant: <i>In the blister carton label, replace (b) (4) with the following condition: “Store below 30 °C (86 °F)”.</i>
Bar code (21CFR 201.25)	Available	Available
Name of manufacturer/distributor	Manufactured in India for: TB Alliance New York, NY 10005	Manufactured by: Mylan Laboratories Limited Hyderabad - 500 096, India Manufactured for: TB Alliance New York, NY 10005
And others, if space is available	N/A	N/A

Reviewer’s Assessment of Labels: {Adequate/Inadequate}

On April 20, 2019, Dr. Millie Shah from DMEPA issued the following comments:

FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day.

FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYYMMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

Revise the human-readable portion of the product identifier to the following format in accordance with the DSCSA:

NDC: [insert product's NDC]

SERIAL: [insert product's serial number]

LOT: [insert product's lot number]

EXP: [insert product's expiration date]

For carton and container labels, the following statement should be communicated to the applicant:

*In the carton and container labels, replace [REDACTED] (b) (4) with the following condition:
"Store below 30 °C (86 °F)".*

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

➤ ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies:

The following comments should be communicated to the applicant.

1. In section 11 Description, list USP/NF names of excipients in alphabetical order (USP <1091>).
2. In section 16 How Supplied/Storage and Handling, remove [REDACTED] (b) (4) and use the following sentences:
"Store below 30 °C (86 °F). Dispense only in original container. Keep container tightly closed".

3. In Medication Guide for the section of How should I store (b) (4)
(b) (4), replace (b) (4)
(b) (4) with the following:
“Store below 30 °C (86 °F). Dispense only in original container. Keep container tightly closed”.
4. In the HDPE bottle and blister pack carton labels and HDPE container label, replace (b) (4) with the following condition:
“Store below 30 °C (86 °F)”.

Overall Assessment and Recommendation:

The PI and labels for cartons and containers are adequate upon resolving the above issues.



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Balajee
Shanmugam

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ATTACHMENT I: Final Risk Assessments

[IQA Review Guide Reference](#)

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	Formulation, raw materials, process parameter, scale/equipment site	L		Acceptable	
Physical Stability	Formulation,	M	(b) (4)	Acceptable	
Content Uniformity	Formulation, raw materials, process parameter	M		Acceptable	
Microbial Limits	Formulation, raw materials	L		Acceptable	
Dissolution	Formulation, raw materials, process	M		Acceptable	

	parameters		(b) (4)		



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