CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210910Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210910
Review # 1

Drug Name/Dosage Form	Aemcolo/Rifamycin delayed release tablets
Strength	194 mg of rifamycin (equivalent to 200 mg of rifamycin sodium)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Cosmo Technologies Ltd
US agent, if applicable	Steven A. Kradjian, RAC, Conventus Biomedical Solutions, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (eCTD 000)	03/16/2018	All
Amendment (eCTD 006)	05/16/2018	Drug Product
Amendment (eCTD 007)	05/22/2018	Biopharmaceutics
Amendment (eCTD 010)	06/08/2018	Process
Amendment (eCTD 011)	07/10/2018	Process
Amendment (eCTD 014)	07/16/2018	Drug Product and Biopharmaceutics
Amendment (eCTD 019)	07/31/2018	Biopharmaceutics
Amendment (eCTD 020)	08/08/2018	Drug Product
Amendment (eCTD 021)	08/13/2018	Drug Product and Drug Substance

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Ben Zhang	Charles Jewell
Drug Product	Thomas Wong	Balajee Shanmugam
Process	Xiumei Ruan	Steven Frisbee
Microbiology	Xiumei Ruan	Steven Frisbee
Facility	Xiumei Ruan	Derek Smith
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Environmental Assessment*	Thomas Wong	Balajee Shanmugam

Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Englund	

** Environmental Assessment is captured in Drug Product Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)			Rifamycin Sodium	Adequate	07/13/2018	Review by Ben Zhang

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104034	Rifamycin

2. CONSULTS

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

Executive Summary

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, rifamycin delayed release tablets. 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 July 18, 2018. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

There are no FDA approved drug products containing rifamycin, but rifamycin has been approved in Europe and has a European Pharmacopeia monograph. The proposed drug product in NDA 210910 is a delayed-release tablet indicated for the treatment of traveler's diarrhea (see table below). The tablet's enteric coating is pH resistant and designed to break down above pH 7. (b) (4) . The product was developed to release rifamycin in the colon.

Proposed Indication(s) including Intended Patient Population	Treatment of Traveler's Diarrhea
Duration of Treatment	The recommended dose is 388 mg (two 194 mg tablets) taken orally twice daily for three days
Maximum Daily Dose	776 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The chemistry, manufacturing and controls (CMC) information for the drug substance in support of this NDA is provided via a reference to DMF (b) (4) held by (b) (4) (b) (4). This DMF was found adequate. Most CMC information for the drug substance was referenced to the DMF, but the drug substance specifications and batch analysis for 3 batches of the drug substance were provided in the NDA. The retest period

of the drug substance is (b) (4) months when stored at a temperature between (b) (4) in (b) (4)

The drug substance specifications were updated in the 08/13/2018 amendment and the only change was to tighten the acceptance criteria of (b) (4) from (b) (4) (copied below). The acceptance criteria of (b) (4) is now the same in both the drug substance and drug product specifications. Following discussion with Ben Zhang, Ph.D., the updated specifications are acceptable.

Table 3. Cosmo Incoming Acceptance Specifications for Rifamycin Sodium

Test	Specifications	Method
TESTS TO Ph.Eur		
Appearance	Fine or slightly granular red powder	Current Ph.Eur. monograph 0432 (Visual)
Identification: Test A	The IR spectrum of the sample is similar to that obtained with the reference substance	Current Ph.Eur. 2.2.24 (IR)
Identification: Test B	Complies with identification test of sodium.	Current Ph.Eur. 2.3.1 (Precipitation)
pH	(b) (4)	Current Ph.Eur. 2.2.3 (Potentiometric determination)
Absorbance: - Maximum of absorbance - Specific absorbance at the maximum	Meets the requirements (b) (4) (b) (4) with reference to the (b) (4)	Current Ph.Eur. monograph 0432 (UV)
Related substances: (b) (4)	NMT (b) (4) NMT NMT	Current Ph.Eur. monograph 0432 (HPLC)
Water	(b) (4)	Current Ph.Eur. 2.5.12 (Semi-micro determination)
Assay	Not less than (b) (4) with reference to the (b) (4)	Current Ph.Eur. 2.7.2 (Microbiological method)
Additional Specifications for CKD Material According to CEP		
Related substances: - Any unspecified impurities	NMT (b) (4)	Current Ph.Eur. monograph 0432 (HPLC)
Residual solvents: (b) (4)	Not more than (b) (4) Not more than Not more than NMT (b) (4)	GC in house method

The drug product is a delayed-release oral tablet that contains 194 mg rifamycin (equivalent to 200 mg rifamycin sodium). It is a yellow brown, ellipsoidal enteric film coated tablet debossed with "SV2" on one side. The enteric coating is a pH-resistant

polymer film which breaks down above pH 7. (b) (4) a multi-matrix system comprised of (b) (4) designed to release rifamycin in the colon (b) (4)

Adequate information on the components and composition of the tablet were provided. The excipients in the formulation are common, compendial grades, and are widely used in the pharmaceutical industry. The quantities of the excipients were above the Inactive Ingredient Database (IID) limits based on a maximum daily dose of 776 mg of rifamycin (equivalent to 800 mg of rifamycin sodium). The levels of these excipients were considered qualified by the pharmacology/toxicology reviewer Tessie Alapatt, Ph.D. The drug product specifications include tests and acceptable limits for appearance, identification, assay, uniformity of dosage units, related substances, and dissolution. Several of the specified impurities are above the qualification threshold. Tessie Alapatt, Ph.D. considered these impurities qualified. Refer to the pharmacology/toxicology review for the evaluation of the excipients and impurities.

The drug product specifications were updated in the 08/08/2018 amendment with a revised dissolution acceptance criteria per recommendations from the biopharmaceutics reviewer (copied below). The only change from the specifications in Thomas Wong's drug product review is for the dissolution method. Th drug product specifications are acceptable.

TEST	Reference Method	Acceptance Criteria
APPEARANCE	Visual inspection	Yellow brown, ellipsoidal, film coated tablets debossed on one side with "SV2"
RIFAMYCIN SV IDENTIFICATION [1]	HPLC In house method CQ-07-0675	Positive (The retention time of the main peak in the sample chromatogram does not differ from that of the Rifamycin SV peak in the standard chromatogram by more than (b) (4)
RIFAMYCIN SV IDENTIFICATION [1]	UV-VIS In house method CQ-07-0675	Positive (The UV spectrum of the sample corresponds to that of the standard)
UNIFORMITY OF DOSAGE UNITS [1]	USP<905>	Complies with USP<905>
RIFAMYCIN SODIUM ASSAY	HPLC In house method CQ-07-0675	(b) (4)
RELATED SUBSTANCES: (b) (4)	HPLC In house method CQ-07-0675	NMT (b) (4) NMT NMT NMT NMT NMT NMT
DISSOLUTION TEST	USP <711> In house method CQ-07-0675	pH 1 — After 2 hours — NMT (b) (4) pH 7.2 — After 1 hour — NMT After 3 hours — NLT After 4 hours — NLT (b) (4) Q)
(b) (4) (b) (4)	(b) (4)	(b) (4)
(b) (4)		

(b) (4)		
Microbiological Analysis **Total Aerobic Microbial Count (TAMC)** **Total Yeasts and Molds Count (TYMC)** **Escherichia Coli**	USP <61> and <62>	NMT (b) (4) NMT Absent from (b) (4)

1. Test performed at release and on stability at T=0 only.
2. (b) (4) tests will be performed on every 10th batch, or one batch per year, whichever occurs first.

USP = United States Pharmacopoeia;
NMT= Not more than;
NLT = Not less than

The drug product review by Thomas Wong, Ph.D. was finalized on 07/22/2018. The applicant submitted an amendment on 07/16/2018 in response to an IR from the biopharmaceutics reviewer recommending the use of an HPLC method in place of the UV method for quantification of the dissolution samples. Since this amendment was not covered in the drug product review, it will be covered in this executive summary. The applicant responded that the UV dissolution method quantifies both rifamycin and the degradant (b) (4) The measured quantities dissolved of both rifamycin and (b) (4) were consistent between the HPLC and UV methods. The applicant included an adequate description of the UV method in 3.2.P.5.2, and this method was validated at both the pH 1 and pH 7.2 conditions. In both pH 1 and 7.2, this method was validated for specificity, LOQ (3%), accuracy, linearity, range, repeatability, intermediate precision, and robustness. At pH 1, the range was evaluated up to 30%, at pH 7.2, the range was evaluated up to 120%. The description and validation of the UV method is adequate. The applicant's response to the IR that justified using UV for the dissolution method is acceptable.

The tablets are packaged in blister packaging system composed of a (b) (4) aluminum foil, containing 12 tablets per blister pack. The secondary packaging system is a carton. The proposed 36-months expiry dating when packaged into the commercial packaging configuration and stored at 20°C to 25°C is acceptable. It is based on the satisfactory stability data of the registration batches on 36-months of the long term stability studies.

The proposed manufacturing process consists of the following steps: (b) (4) (b) (4) (b) (4) is the key process used to manufacture Rifamycin Tablets. Three NDA batches were manufactured at (b) (4) kg (or (b) (4) tablets), and the same production scale is proposed for intended commercial runs.

In-process controls have been established for critical manufacturing steps, which include (b) (4)

(b) (4)

Following a review of the application, inspectional documents, and pre-approval inspection results, all listed facilities for NDA 210910 are found to be acceptable for their proposed manufacturing and/or testing operations. There are no significant, outstanding manufacturing or facility risks that prevent the approval of this application.

The Biopharmaceutics review focused on (1) the evaluation of the adequacy of the information/data supporting the proposed dissolution method and acceptance criteria, (2) the alcohol dose-dumping potential of the proposed drug product, (3) bridging throughout product development, and (4) providing a recommendation concerning a delayed or extended release claim for the labeling. The proposed dissolution method and acceptance criteria were revised per FDA's recommendations. The final approved dissolution method and acceptance criteria for batch release and stability testing are captured in the drug product specifications above. The results of the in-vitro alcohol studies indicate that there is alcohol induced dose dumping at the first 1 h time point with concentrations of >10% alcohol, at pH 7.2. Labeling recommendations were communicated to the Clinical Pharmacology and Clinical Reviewers. The formulation and manufacturing site proposed for the commercial drug product are the same as those used for the phase 3 clinical batches. Therefore, bridging was not needed. Finally, the proposed product is considered a delayed-release tablet, and the description of extended release is not needed.

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendations were conveyed to the OND PM for consideration as the labeling is finalized:

The strength of the product should be expressed in terms of the USP salt policy: 194 mg of rifamycin (equivalent to 200 mg rifamycin sodium).

We recommend that the non-proprietary name for the product be: rifamycin delayed-release tablets. The USAN is rifamycin, not the proposed rifamycin SV.

See the labeling review for the complete list of recommendations to OND.

D. Final Risk Assessment

See Attachment

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BIOPHARMACEUTICS

NDA: 210910
Drug Product Name/Strength: AEMCOLO® (rifamycin sodium) delayed-release tablets, 200 mg
Route of Administration: Oral
Dosage Form: Delayed release tablets.
Applicant Name: Cosmo Technologies Ltd.
Intended for Use: Treatment of Travelers' Diarrhea (TD)
Submission Type: 505(b)(1) (NME)
PDUFA Goal Date: 11/16/2018

REVIEW SUMMARY

The Rifamycin MMX tablet is an oral formulation of rifamycin sodium utilizing Cosmo's patented multi-matrix (MMX) formulation comprised of a delayed-release coating (b) (4) that assure the release of rifamycin in the colon where it is locally acting, with low systemic bioavailability. Each tablet contains 200 mg of (b) (4) rifamycin sodium (equivalent to 194 mg rifamycin). The recommended Rifamycin MMX dosing regimen for TD is 400 mg (as (b) (4) rifamycin sodium salt) twice daily (BID) for 3 days. The clinical program in support of this NDA for the proposed indication of TD includes 3 phase 1 pharmacokinetic (PK) studies, 2 phase 2 studies and 2 randomized, double-blind phase 3 studies.

The Biopharmaceutics review is focused on (1) the evaluation of the adequacy of the information/data supporting the proposed dissolution method and acceptance criteria, (2) the alcohol dose-dumping potential of the proposed drug product, 3) bridging throughout product development, and (4) providing a recommendation concerning a delayed or extended release claim for the labeling.

1) ***Dissolution Method and Acceptance Criteria:*** The proposed dissolution method and acceptance criteria have been revised as per FDA's recommendations. The final approved dissolution method and acceptance criteria for batch release and stability testing are shown in the table below.

USP Apparatus	Speed (RPM)	Medium	Acceptance Criteria
II (Paddle)	100	Sequential two-stage testing: 1. Acid stage: HCl 0.1 M with 0.5% w/v Macrogol Cetostearyl Ester, 1000 mL/37°C 2. Buffer stage: pH 7.2 Sodium Phosphate buffer, 900 mL/37°C	Acid stage: 2 h: NMT (b) (4)% Buffer stage*: 1 h: NMT (b) (4)% 3 h: NLT (b) (4)% 4 h: NLT (b) (4)% (Q)

*on the same tablet but restarting the clock

2) ***Alcohol Dose-Dumping Potential:*** The results of the in-vitro alcohol studies indicate that there is alcohol induced dose dumping at the first 1 h time point with concentrations of >10% alcohol, at pH 7.2. It is noted that the language regarding alcohol intake has not been included in the labeling of the proposed drug product. Based on the available in vitro dissolution data, the proposed drug product may lose colon targeting in the presence of alcohol. We defer to the Clinical Pharmacology Reviewer and the Clinical Reviewer to consider adding labeling instruction such as: "do not take with alcohol" under the Dosage and Administration section of the label.

3) ***Bridging of Formulations:*** The proposed commercial drug product formulation and image are the same as the drug product formulation and image used in the phase 3 clinical studies. The manufacturing site of the clinical batches is also the proposed commercial site. Therefore, bridging between the clinical and commercial products was not needed.

4) Extended Release Claim: The proposed drug product is deemed a "delayed release tablet" from a Biopharmaceutics standpoint. Extended release claim is not required nor applicable for this delayed release locally acting drug product.

BIOPHARMACEUTICS REVIEW RECOMMENDATION: **Adequate**

From the Biopharmaceutics perspective, NDA 210910, for AEMCOLO® (rifamycin sodium) delayed-release tablets, 200 mg, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang, PhD **8/10/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Elsbeth Chikhale, PhD **8/10/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (1)	3/16/2018	Original submission
0007 (7)	5/22/2018	Quality/Response to information request dated 5/11/2018
00014 (14)	7/16/2018	Quality/Response to information request dated 6/27/2018
0019 (19)	7/31/2018	Quality/Response to information request dated 7/30/2018

➢ *DRUG PRODUCT*

The proposed drug product is developed to target its bactericidal action in the colon with low systemic bioavailability of the drug substance. The tablet is a multi-matrix system with a (b) (4) enteric film coating (b) (4) .

(b) (4)

After the pH dependent film-coating is dissolved when reaching a pH 7 or higher environment, (b) (4)
(b) (4)

➢ *BCS DESIGNATION*

A BCS designation request for the proposed drug product has not been submitted to FDA nor is required.

- ***Solubility:*** The provided solubility data indicate that rifamycin exhibits low solubility at acidic pHs but high solubility above pH 5 (**Table 1**).
- ***Permeability:*** Permeability information was not provided in the submission.

➢ *DISSOLUTION INFORMATION*

Applicant's Proposed Dissolution Method and Acceptance Criteria*:* The originally proposed dissolution method and dissolution acceptance criteria for the proposed drug product are presented below.

USP Apparatus	Speed (RPM)	Medium	Acceptance Criteria
II (Paddle)	100	(b) (4) two-stage testing: 1. Acid stage: 0.1 M HCl with 0.5% w/v Macrogol Cetostearyl Ester, 1000 mL/37°C 2. Buffer stage: pH 7.2 Sodium Phosphate buffer, 900 mL/37°C	Acid stage: 2 h: NMT (b) (4)% Buffer stage: (b) (4)

Dissolution Method Development:

(b) (4)

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(b) (4)

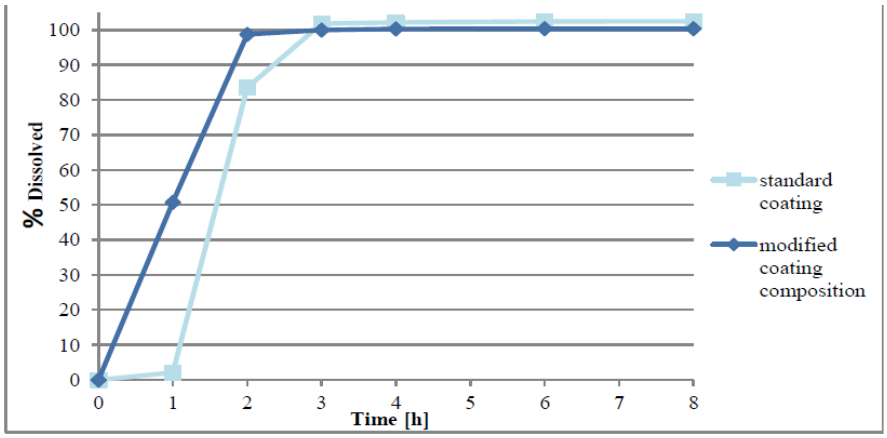
[redacted]

Discriminating Capability of the Dissolution Method:

- ***Coating*** (b) (4)***:*** The proposed dissolution method was shown to be sensitive to the changes of composition of the film coating. Specifically, at pH 7.2, the tablet coated with a (b) (4) had a faster dissolution profile than the tablet coated with (b) (4) (**Figure 3**). No effect was observed on dissolution profiles of the tablets in 0.1 M HCl (b) (4).

Figure 3: Effect of Coating Composition on Dissolution Profile of Rifamycin sodium Tablets 200 mg Using Apparatus 2 at 100 RPM in pH 7.2 Buffer

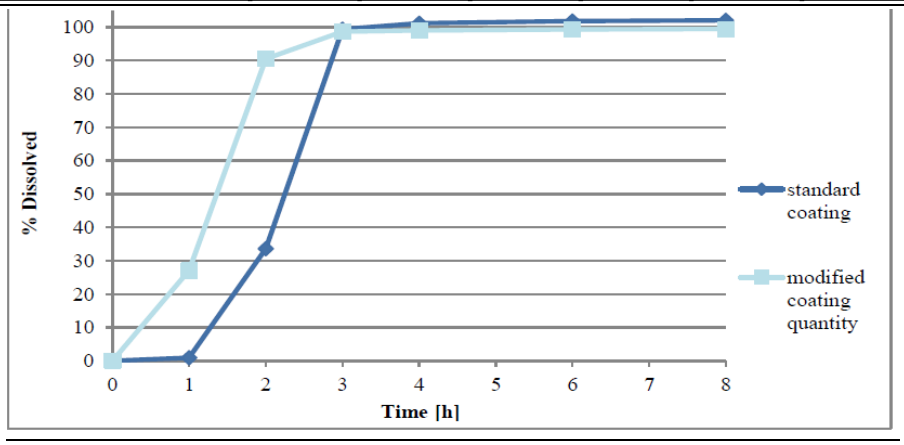
Comparison	Rifamycin sodium dissolved (n=6) (%)					
	1h	2h	3h	4h	6h	8h
Standard coating composition (b) (4)	2	84	102	102	102	103
Modified coating composition (b) (4)	51	99	100	100	100	100



- ***Coating Weight:*** Significant difference in release rate was observed between the standard ((b) (4) (b) (4) mg/tablet) and the modified ((b) (4) mg/tablet) quantities of film coating (**Figure 4**). Film coating weight of (b) (4) mg/tablet failed the proposed acceptance criteria at 1 h time point of NMT (b) (4) % limit.

Figure 4: Dissolution Profiles of Rifamycin sodium Tablets, 200 mg (Batch DI127, Supportive Batch) with Different Amounts of Film Coat Using Apparatus 2 at 100 rpm in pH 7.2 Buffer

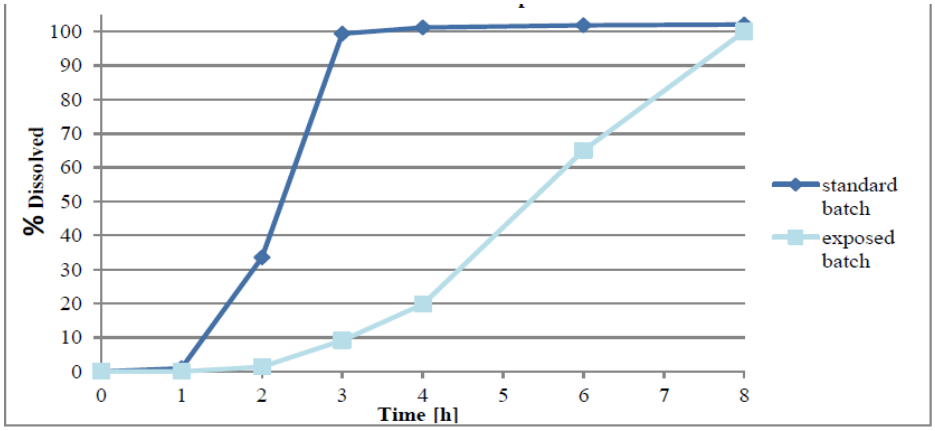
Comparison	Rifamycin sodium dissolved (n=6) (%)					
	1h	2h	3h	4h	6h	8h
Standard coating quantity ((b) (4) mg/ tablet)	1	34	99	101	102	102
Modified coating quantity ((b) (4) mg/tablet)	27	91	99	99	99	100



- ***Stability Samples:*** Drug release is shown to be slower for tablets exposed to high stress conditions (60°C for 7 days) compared to that for an unstressed control sample (**Figure 5**).

Figure 5: Dissolution Profiles of Rifamycin Tablets, 200 mg, Batch DI127 Stored For 7 Days Under 60°C (Exposed Batch) Versus Unstressed Control Samples (Standard Batch)

Comparison	Rifamycin sodium dissolved (n=6) (%)					
	1h	2h	3h	4h	6h	8h
Standard batch	1	34	99	101	102	102
Exposed batch (60°C for 7 days)	0	1	9	20	65	100



Validation of Dissolution Method:

An UV assay method (with UV detection at 299 nm in acid and 314 nm in buffer) is used to quantify the drug in the dissolution samples. (b) (4) (b) (4) (b) (4) Therefore, this reviewer considers the UV method is inappropriate, and an analytical HPLC method for the quantitation of the dissolution samples is recommended. In response to the IR comment #7 regarding this issue (See the section of "Biopharmaceutics Information Requests" in this review), the Applicant provided data to justify the use of UV instead of HPLC for dissolution testing. The Drug Product Reviewer has determined that the UV method is acceptable based on the provided information. Refer to the Drug Product Review, for the evaluation of the UV method for dissolution testing at pH 1 and pH 7.2.

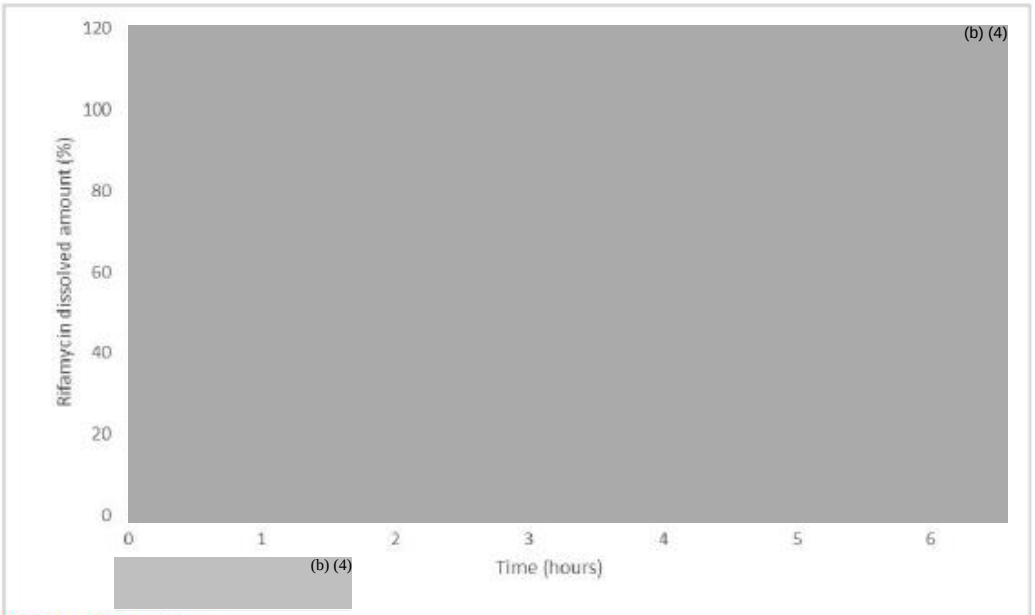
The dissolution method robustness is validated with respect to dissolution medium composition (± 0.2% of surfactant), media pH (± 0.1 pH unit), and degassing of the dissolution media.

(b) (4) ***. Sequential Testing:***

(b) (4) (b) (4) for delayed release drug products, the FDA recommends that

the dissolution testing be conducted in sequential order using the same unit-tablets, (b) (4) (b) (4). In response to the IR comment #6, the Applicant has agreed with the FDA's recommendation to perform the dissolution test in a sequential order for commercial products. In addition, the Applicant (b) (4) using the same batch and confirmed the dissolution performance produced by sequential testing (b) (4) (b) (4) (**Figure 6**).

Figure 6: (b) (4) pH 7.2 Buffer Stage Dissolution Data for (b) (4) Sequential Testing (After Acid Stage), Batch GL035



Acid stage data not shown.

Reviewer's Assessment: ***ADEQUATE***

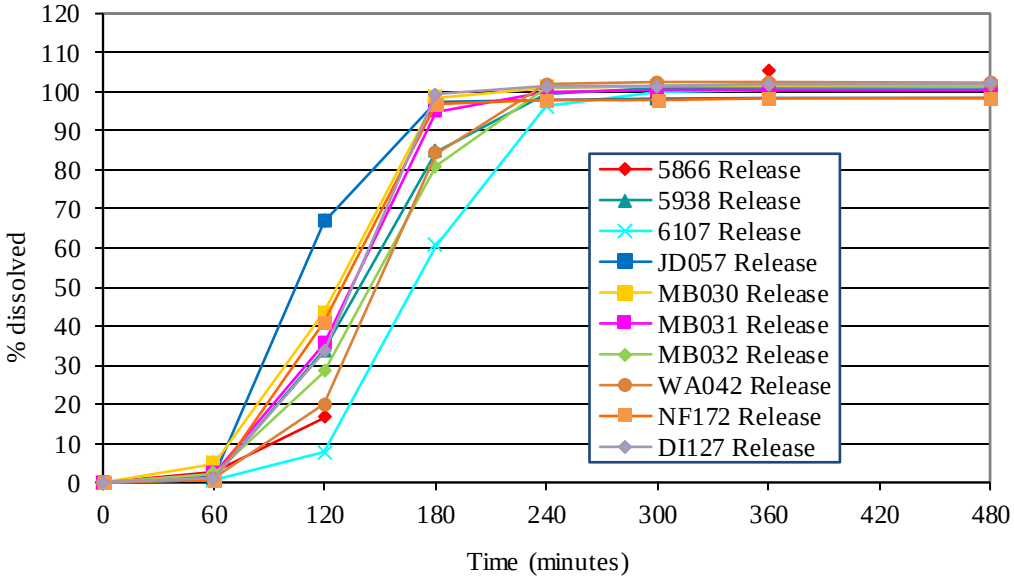
Overall, the proposed dissolution method is validated and it is considered adequate for quality control purposes based on the availability of sufficient sink condition and complete dissolution, as well as, discriminating ability of the method towards critical manufacturing variables (e.g. enteric coating).

Dissolution Acceptance Criteria:

Acid stage: The proposed dissolution acceptance criterion for the acid stage of NMT (b) (4)% at 2 h is acceptable, based on the provided dissolution data at pH 1.

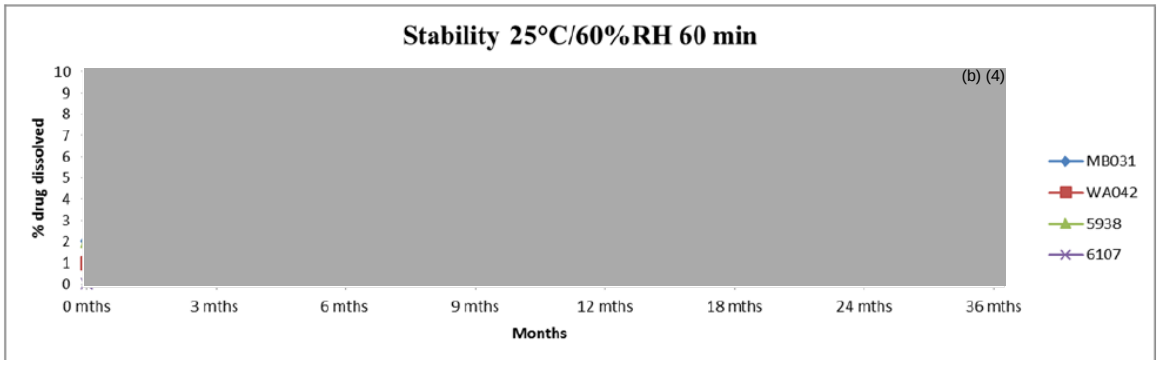
Buffer stage: The dissolution profile data with sampling time points: 1, 2, 3, 4, 5, 6, and 8 hours collected from all the clinical and registration batches at lot release are summarized in **Figure 7**. The summary for each dissolution sampling time point from 4 clinical batches over the proposed 36 month expiry period under long-term storage conditions are also provided (**Figure 8**).

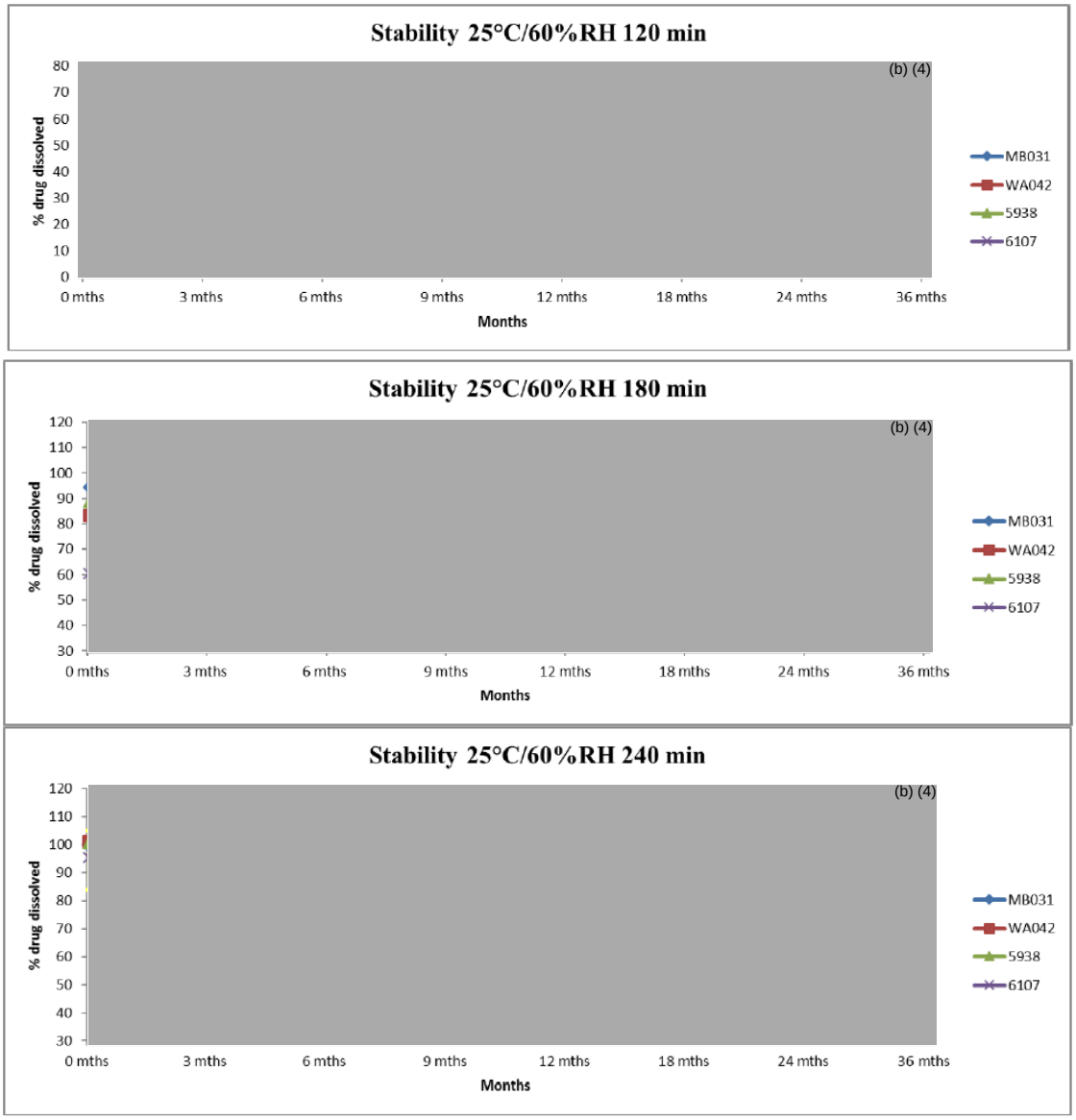
Figure 7: Summary of In Vitro Dissolution Data at Batch Release in pH 7.2 Using Apparatus 2 at 100 rpm



Notes: Batches 5866, 6107 were used in the phase 1 studies; Batch 5938 were used in the phase 2 studies; Batches WA042, JD057, NF172, and MB030 were used in the phase 3 studies, and Batches MB030, 031 and 032 are registration batches. Batch DI127 is supportive batch used in the dissolution test.

Figure 8: Summary of In Vitro Dissolution Data at Long Term Stability Testing in pH 7.2 Using Apparatus 2 at 100 rpm





Dates of the approximate period of clinical trial utilization are indicated with dashed lines within the curve for each batch. The ranges experienced in clinical trials are highlighted in yellow.

The originally proposed and newly proposed dissolution acceptance criteria for the buffer stage of NMT (b) (4)% at 1 h and NLT (b) (4)% (Q) at (b) (4)h (original) or 4 h (new) (*Notes: The last time point was at* (b) (4)*h in the original submission. The Applicant had modified it to 4 h during the review cycle*), are unacceptable, for the following reasons:

1. For the first-time point of 1 h, less than 5% of drug release were obtained for all the clinical batches and exhibit batches at release and stability.
2. For the last time point of 4 h, all the clinical batches and exhibit batches at release reached more than 85% drug release, on average, at 4 h. Although there are some failures at the last

stability time point (36 months) at S1, all batches, including batch WA042, would pass at S2 (worst case scenario).

3. To describe the slowly dissolving characteristics of the dissolution profile (i.e. complete dissolution reached at 4 h), an additional time point for the intermediate phase is necessary for the quality control. An acceptance criterion with a one-sided limit instead of range for the middle time point is more appropriate for this case, as there is a high dissolution variation across the clinical batches at the intermediate time points. Therefore, the following revised dissolution acceptance criteria for the buffer stage were recommended in a IR letter dated 7/30/2018:

Sampling time	***Originally Proposed Acceptance***	***Recommended Acceptance***
1 hour	*NMT* (b)(4)%	*NMT* (b)(4)%
3 hour	*None*	*NLT* (b)(4)%
4 hour	*NLT* (b)(4)% *(Q)*	*NLT* (b)(4)% *(Q)*

On 7/31/2018, the Applicant has agreed to the FDA's recommended acceptance criteria, and the Applicant provided the revised drug product specifications table with the updated acceptance criteria for the dissolution test on 8/8/2018.

Reviewer's Assessment: **ADEQUATE**

Based on the provided dissolution data, the proposed revised dissolution acceptance criteria of < (b)(4)% of drug released at 2 h for acid stage, and < (b)(4)% at 1 h, > (b)(4)% at 3 h, and (b)(4)% (Q) at 4 h for buffer stage are acceptable.

- ***IN-VITRO ALCOHOL DOSE DUMPING***

The potential dose dumping is considered an efficacy and safety issue for this delayed release drug product. Since this drug product is locally acting with low systemic absorption, the in vitro alcohol dose dumping studies are critical to predict the potential for in vivo dose dumping.

In the original submission, the Applicant provided dissolution data only for 40% ethanol in 0.1 N HCl. However, per the current FDA's practice, additional in vitro studies are required to evaluate the potential for alcohol dose dumping, with 0%, 5%, 10%, 20%, and 40% alcohol concentrations in both acid and buffer stages, for the following reasons:

1. The alcohol dosing dumping effect can be alcohol concentration independent or dependent;
2. Ethanol is absorbed through the GI tract. When alcohol is consumed, it enters the stomach, where it can be absorbed into the bloodstream. However, if no food is present, most of the alcohol moves down into the small intestine where there is a much larger surface area for absorption compared to the stomach.

Upon request, the Applicant provided the updated study report on 7/16/2018. The results of the studies are summarized in **Figure 9 and Table 5**.

Figure 9: Dissolution Profiles of Rifamycin Sodium MMX Tablets, 200 mg, Lot GL036 in Various Ethanol Concentrations Tested Sequential For 2 Hours In Acid Medium and Then in pH 7.2 Buffer Medium

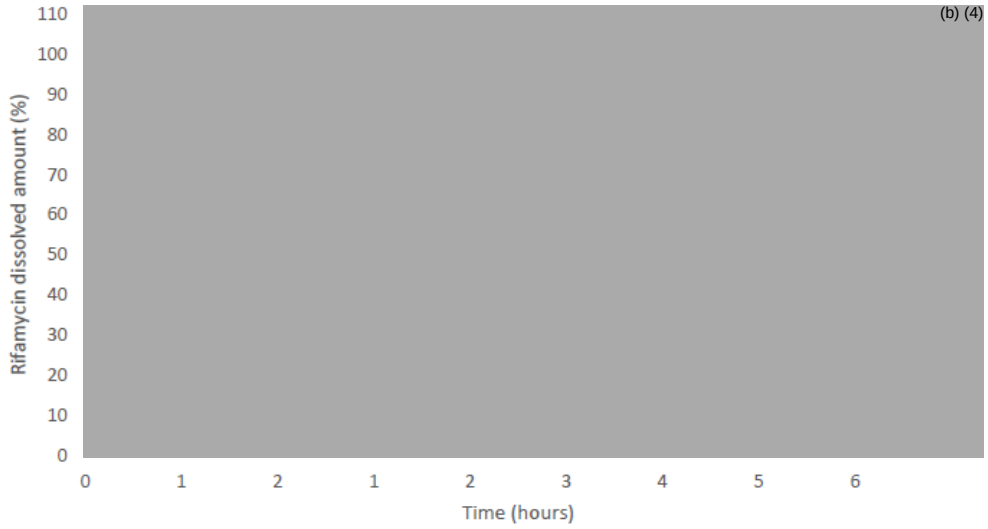


Table 5: Comparison of Dissolution Profiles

Sample	MSD upper confidence limit 90% (CL90)	Results acceptance criterion: CL90 ≤ 4.6
Test 1 (ethanol 5%)	3.3	PASS
Test 2 (ethanol 10%)	6.0	FAIL
Test 3 (ethanol 20%)	7.3	FAIL
Test 4 (ethanol 40%)	18.2	FAIL

Notes: Multivariate confidence region procedures were used by the Applicant for comparing dissolution profiles for the buffer stage due to the high within-batch variation for the early time points 1 h and 2 h (>15%). The MSD (Multivariate Statistical Distance) calculated by the Applicant is 4.6.

Acid stage: The results from the in vitro alcohol dissolution testing indicate that there is no dose dumping at the acid stage. All the test samples had <3% drug release after 2 h in 0.1 M HCl with different alcohol concentrations.

Buffer stage: The results showed that with increasing amounts of alcohol, there is in vitro dose dumping at the buffer stage, specifically, the presence of increasing amount of ethanol at 10%, 20% and 40% (Test 2, 3, and 4), increases the dissolution rate of the proposed drug product at the first 1 h and intermediate 2 h time points, and the dissolution profiles with 10%, 20% and 40% alcohol failed the MSD similarity testing.

Reviewer's Assessment: ADEQUATE

The results of the in-vitro alcohol studies indicate that there is alcohol induced dose dumping at the first 1 h time point with concentrations of >10% alcohol at pH 7.2. It is noted that the language regarding alcohol intake has not been included in the labeling of the proposed drug product. Based on the available in vitro dissolution data, the proposed drug product may lose colon targeting when taken with alcohol. We defer to the Clinical Pharmacology reviewer and the Clinical reviewer for the recommendation regarding the potential risk or clinical consequence of concomitant use of alcohol, and to consider adding a clear labeling instruction with "do not take with alcohol" under Dosage and Administration section of the label.

- ***BRIDGING OF FORMULATIONS***

Reviewer's Assessment: ADEQUATE

The proposed commercial drug product formulation is the same as the drug product formulation of the clinical batches used in the phase 3 efficacy studies, including the image. The manufacturing site of the clinical batches is also the proposed commercial site. Therefore, bridging between the clinical and commercial formulation products is not needed.

It's noted that there is no PK data collected in the phase 3 studies as the proposed drug product is locally acting with very low systemic absorption. Comparative dissolution profiles were deemed not necessary to support bridging (i.e., the change of the image) between the early phase 1 PK (Batch 6107, not debossing) and the phase 3 clinical and registration batches (debossed on one side with "SV2").

- ***EXTENDED RELEASE CLAIM***

During the review cycle, issue arose as to whether the proposed drug product is a delayed release or a combination of delayed and extended release product. The term of "extended-release" was used in the original submission, including the clinical report, in addition, based on the in vitro dissolution performance, the proposed drug product exhibits properties of delayed-release followed by slow extended-release.

In the mid-cycle meeting with the Applicant on 07/06/2018, the Applicant claimed that the proposed drug product is a delayed release product only and clarified that the term extended release was used in error. To support the claimed delayed release, the Applicant provided explanations, specifically:

- The proposed formulation was designed to achieve gastro-resistance (2 hours in acid medium) and a further delay in the release of approximately 1 hour in buffer stage, to allow the tablet to reach the target organ (the colon) before releasing the (b) (4) active ingredient.

- After the release delay, [redacted] (b) (4) a complete release of the active ingredient within approximately 3-4 hours in a pH 7.2 buffer.
- Controlled extended release is not considered necessary for non-absorbable Rifamycin for the proposed indication of TD after the delayed release.
- The lack of [redacted] (b) (4) justifies the variability of drug concentrations obtained at intermediate time points of 2 and 3 hours in the buffer stage. Such variability has been observed during pivotal clinical trials without jeopardizing product efficacy.

This reviewer agrees with the Applicant that based on the provided information, the proposed drug product is a delayed release drug product.

Reviewer's Assessment: Not Applicable

Overall, from the Biopharmaceutics perspective, the dosage form of the proposed drug product is "Delayed Release Tablets". An extended release claim is not required nor applicable for this locally acting drug product.

- **OVERALL RECOMMENDATION: Adequate**

From the Biopharmaceutics perspective, NDA 210910, for AEMCOLO® (rifamycin sodium) delayed-release tablets, 200 mg, is recommended for **APPROVAL**.

LIST OF BIOPHARMACEUTICS INFORMATION REQUESTS (IRs)

IRs dated 5/11/2018:

1. Provide additional drug substance solubility data at 37°C between the pH range of 1 to 7.
2. The dissolution method development report (TEST 17-1-02 Rev. 01) is missing some critical details. Cleary specify the testing conditions (medium volume, pH, rotation speed, etc.) and batch numbers/age of batch at time of dissolution testing associated with each dissolution test, each data set, each Table and each Figure described in the report. Update and resubmit the dissolution method development report.
3. Provide complete dissolution profile data (n=12, individual, mean, RSD, and profiles with the time points of 1h and 2h at acid stage, and 1h, 2h, 3h, 4h, 6h, and 8h at buffer stage) for the clinical and registration batches collected during batch release and stability studies.
4. To support bridging between debossed and not debossed the drug product tablets, provide comparative multipoint dissolution profile data (debossed vs. not debossed tablets) obtained using the proposed dissolution method.
5. Submit the complete dissolution profile data in ".xlsx" or ".xpt" format.

IRs dated 6/27/2018:

6. (b) (4)
7.
8.
9. (b) (4) Propose a minimum of three sampling time points and acceptance limits for the buffer stage. The last sampling time point should be selected where (b) (4) % drug release occurs. Include a detailed discussion of the data supporting your justification for the proposed dissolution acceptance criteria. Provide figures for each dissolution sampling time point and highlight the dates of the clinical trial utilization period over the entire proposed 36 months expiry period under long-term storage conditions.
10. The information included in the in vitro alcohol dose dumping report (17-1-01 Dissolution in Ethanol) is incomplete, because when alcohol is consumed, it enters the stomach, where it can

be absorbed into the bloodstream; however, if no food is present, most of the alcohol moves down into the small intestine where there is a much larger surface area for absorption compared to the stomach. Therefore, we recommend that you conduct additional in vitro studies evaluating the in vitro alcohol-induced dose dumping potential of your proposed drug product in both, acid and buffer phases and different concentrations of alcohol and provide the following information/data:

a) Complete dissolution profiles (n=12, individual, mean, SD, comparison plots) using 0%, 5%, 10%, 20%, and 40% alcohol concentrations in the proposed dissolution media (both acid and buffer stages) using the proposed testing conditions (apparatus and speed) and sequential testing (same unit-tablets).
b) The similarity (or lack thereof) between the dissolution profiles should be estimated using an appropriate statistical test (e.g., f_2 test). The 0% alcohol dissolution profile data should be used as the reference.

IR dated 7/30/2018:

11. In view of the slow dissolution rate of the proposed Rifamycin MMX tablets at the buffer stage (i.e., complete dissolution achieved at 4 hours), we recommend that three sampling time points for setting the dissolution acceptance criteria. Based on the provided dissolution profile data generated from the pivotal clinical and registration batches, FDA recommends the following revised dissolution acceptance criteria for the buffer stage:

FDA's Recommended Dissolution Acceptance Criteria for Rifamycin MMX tablets 200 mg Buffer Stage	
Sampling time	**% Drug Dissolved**
1 hour	NMT (b) (4)%
3 hour	NLT (b) (4)%
4 hour	NLT (b) (4)% (Q)

Update your drug product release and stability specifications accordingly.

Qi Zhang

Digitally signed by Qi Zhang
Date: 8/10/2018 03:22:08PM
GUID: 547e178000007695c91eb10380b07939

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 8/10/2018 07:20:59PM
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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	AEMCOLO (rifamycin (b) (4)) delayed-release tablets *See reviewer discussion*
Dosage form, route of administration	delayed-release tablets, for oral use *See reviewer discussion*
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	(b) (4) (b) (4) *See reviewer discussion*

2. *Section 2 Dosage and Administration*

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)	There are special instructions not to crush, break or chew the tablet. The tablet is taken with water.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Delayed-release tablet
Strengths: in metric system	(b) (4) mg *Refer to reviewer discussion below*
Active moiety expression of strength with equivalence statement (if applicable)	The salt policy applies to this product.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	AEMCOLO is a yellow-brown, ellipsoidal, film-coated, delayed release tablet debossed on one side with "SV2". Each delayed release tablet contains 194 mg rifamycin (b) (4) (b) (4)

4. *Section 11 Description*

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	AEMCOLO rifamycin delayed release tablets
Dosage form and route of administration	Delayed release tablets, oral
Active moiety expression of strength with equivalence statement (if applicable)	No. Recommended edit includes addition of equivalence statement *Refer to reviewer discussion below*
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>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Not listed
Chemical name, structural formula, molecular weight	The structure, formula and molecular weight for the salt are given. *Refer to reviewer discussion below*
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Recommendation to include color of coat (yellow brown). *Refer to recommended edit in PI*

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Recommended edit to 194 mg
Available units (e.g., bottles of 100 tablets)	Box of 12 tablets Box of 36 tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yellow brown, ellipsoidal and film coated tablets
Special handling (e.g., protect from light)	No special instructions for handling
Storage conditions	Store at 20° to 25°C (68 to 77°F) excursions permitted to 15 to 30°C (59° to 86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: *{Adequate}*

The drug substance is the sodium salt of rifamycin. The strength was originally described as 200 mg (based on the salt form). The drug product review by Thomas Wong, Ph.D. described that the following comment was sent to the applicant to update the labeling to be consistent with the USP salt policy:

The strength expression of the tablets is in sodium salt form and does not comply with the USP salt policy. Refer to the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015 and revise the strength of the tablet accordingly.

The expression of strength was revised to 194 mg (equivalent to 200 mg rifamycin SV sodium salt) in the 05/16/2018 amendment. This revision was found acceptable in the drug product review; however, not all of the labeling was updated to express the strength as 194 mg. The following recommendation will be sent to update the labeling to comply with the USP salt policy.

Update the strength throughout the labeling to 194 mg of rifamycin, to comply with the USP salt policy. The strength should not be expressed as 200 mg, which is based on rifamycin sodium.

The applicant proposed the proprietary name and established name to be: *AEMCOLO (rifamycin SV) delayed-release tablets*. In some sections of the labeling, the established name was described as (*rifamycin SV MMX) delayed-release tablets*. MMX® is described in the NDA as the matrix system of the tablet. The NDA describes the drug substance as both rifamycin SV and rifamycin sodium. The USP dictionary has an entry for rifamycin, and describes rifamycin SV as a code used for rifamycin, but

rifamycin SV is not a recognized USAN. Therefore, SV and MMX should be deleted from the established name. The following recommendation will be shared with OND.

The drug substance is listed as rifamycin in the USP dictionary, not as rifamycin SV. Update the labeling to refer to the drug substance as rifamycin. Rifamycin SV, and rifamycin SV MMX should not be listed in the established name.

The biopharmaceutics reviewer evaluated the supporting evidence for the product to determine whether the product should be described as "delayed-release tablets" or "extended-release tablets". Elsbeth Chikhale, Ph.D. e mailed on 7/17/2018 that based on the preliminary review of the IR response, the description of delayed release tablet is acceptable. Delayed-release tablets are a recognized dosage form in USP <1151>. Refer to the biopharmaceutics review concerning the final determination for the dosage form for this product.

Based on the discussion above, the proprietary name and established name should be expressed as the following in the PI:

AEMCOLO (rifamycin) delayed-release tablets

Currently the dosage form and strength section of the Highlights section reads: (b) (4) The strength should be based on the free acid, and the formatting should be updated to be consistent with the labeling review tool. The following edit will be recommended in this section.

Highlights
DOSAGE FORMS AND STRENGTHS:
Delayed-release tablets: 194 mg of rifamycin

The dosage forms and strengths section of the PI currently reads:

AEMCOLO is a yellow-brown, ellipsoidal, film-coated, delayed release tablet debossed on one side with "SV2". Each delayed release tablet contains (b) (4)

This section should be updated to describe the strength as 194 mg. Our recommended edit is copied below. The reference to the drug substance as (b) (4) was deleted. The strength was written to clearly state that 194 mg is based on rifamycin.

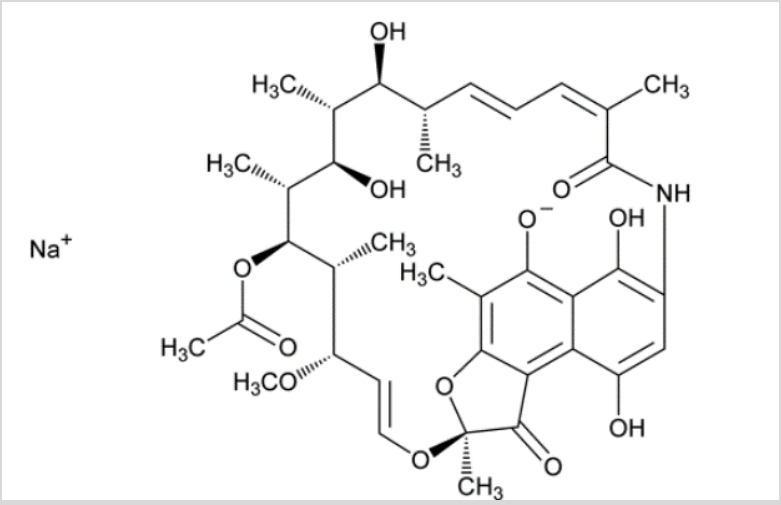
Dosage forms and strengths:
AEMCOLO is a yellow-brown, ellipsoidal, film-coated, delayed release tablet debossed on one side with "SV2". Each delayed release tablet contains 194 mg of rifamycin.

We have several recommended edits for the Description section of the NDA. This section did not include an equivalency statement. The equivalency statement below is recommended for the description section of the NDA:

AEMCOLO, delayed release tablet, for oral administration, contains 194 mg of rifamycin equivalent to 200 mg of rifamycin sodium

The structure of the drug substance in section 11 shows a different (b) (4) The drug substance reviewer Ben Zhang, Ph.D. also agreed that the (b) (4) should be updated to be consistent with the USP structure. A comment will be included in the PI recommending that the structure of the drug substance be updated.

(b) (4)



Structure from USP dictionary (above)

The description section contained a couple of references to the [redacted] (b) (4) The description of [redacted] (b) (4) does not belong in section 11, which is supposed to focus on the description of the product. The proposed edits to this section are copied below.

AEMCOLO, delayed-release tablets are enteric coated with a pH-resistant polymer film which breaks down above pH 7. The tablet core contains rifamycin.

Each tablet contains the following inactive ingredients: ammonio methacrylate copolymer (Type B), ascorbic acid, glyceryl distearate, lecithin, magnesium stearate, mannitol, methacrylic acid and methyl methacrylate copolymer (1:2), polyethylene glycol 6000, colloidal silicon dioxide, talc, titanium dioxide, triethylcitrate, yellow ferric oxide.

The "how-supplied" section was updated to include a salt equivalency statement. The edits are copied below:

AEMCOLO delayed release tablets contain194 mg of rifamycin (equivalent to 200 mg of rifamycin sodium), and are yellow brown, ellipsoidal and film coated. These are packaged in blister cards of 12 tablets contained in a cardboard carton. They are supplied as follows:

NDC (XXXXX-XXX-XX) : box of 12 tablets.
NDC (XXXXX-XXX-XX) : box of 36 tablets

Store at 20° to 25°C (68 to 77°F) excursions permitted to 15 to 30°C (59° to 86°F).

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

The recommendations above will be shared with OND during labeling negotiations.

II. Labels:

1. ***Container and Carton Labels***

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Item	Information provided in the container label (blister packaging)	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Rifamycin (b) (4)	Rifamycin (b) (4) *See reviewer discussion below*
Dosage strength	(b) (4)	(b) (4) *See reviewer discussion below.*
Net contents	Net contents not listed on individual blister sheets	12 or 36 tablets
"Rx only" displayed prominently on the main panel	No	Yes
NDC number (21 CFR 207.35(b)(3)(i))	No	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Space available on panel
Storage conditions	No	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)
Bar code (21CFR 201.25)	No	Space Available
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	N/A	There is a lock and key

Reviewer's Assessment of Labels: *{Adequate}*

A single blister packaging containing 12 tablets was submitted. There are (b) (4) different labels submitted for the carton: (b) (4) commercial cartons with 12 tablets and 36 tablets. (b) (4) This is acceptable.

The carton and blisters both describe the established name as (rifamycin SV MMX®). As described above, the drug substance should be referred to as rifamycin, and not rifamycin SV. In addition, the use a trademarked MMX® in the established name is not acceptable. The applicant should update the established name to be consistent with the PI. Also, as discussed above, the strength should be 194 mg, not 200 mg. The applicant will be informed that they should update the strength and include the salt equivalency statement.

We do not agree with listing the established name as (rifamycin SV MMX®) on the labeling. The drug substance is listed as rifamycin in the USP dictionary, not as rifamycin SV. Update the labeling to refer to the drug substance as rifamycin. Rifamycin SV, and rifamycin SV MMX should not be listed on the labeling.

The strength expression of the tablets is in sodium salt form and does not comply with the USP salt policy. Refer to the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015 and revise the strength of the tablet accordingly. Update the carton and blister labeling to list the strength as 194 mg. In addition, include the salt equivalency statement. Refer to the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances

The blisters do not have "Rx Only" written on them.

Include "Rx Only" on the blister packaging.

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

List of Deficiencies:

The recommended edits to the PI will be shared with OND during labeling negotiations.

The following comments for the container closure system will be shared with DMEPA:

1. *We do not agree with listing the established name as (rifamycin SV MMX®) on the labeling. The drug substance is listed as rifamycin in the USP dictionary, not as rifamycin SV. Update the labeling to refer to the drug substance as rifamycin. Rifamycin SV, and rifamycin SV MMX should not be listed on the labeling*
2. *The strength expression of the tablets is in sodium salt form and does not comply with the USP salt policy. Refer to the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015 and revise the strength of the tablet accordingly. Update the carton and blister labeling to list the strength as 194 mg. In addition, include the salt equivalency statement. Refer to the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances*
3. *Include "Rx Only" on the blister packaging*

Overall Assessment and Recommendation:

Acceptable with the described edits that will be shared with OND and DMEPA.

Primary Labeling Reviewer Name and Date:

Erika E. Englund, Ph.D.

07/20/2018

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

Erika Englund

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Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 7/21/2018 07:42:21PM
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ATTACHMENT I: Final Risk Assessments

IQA Review Guide Reference

A. Final Risk Assessment – NDA 210910

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**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	L	Sufficient evaluation of impurities in the NDA. Adequate acceptance criteria proposed	Acceptable	
Content Uniformity	Formulation Raw materials Process parameters Scale/equipment Site	M	The in-process controls were found acceptable	Acceptable	
Physical Stability	Formulation Raw materials Process parameters Scale/equipment Site	M	Polymorphic conversion was not observed, and submitted stability data was acceptable	Acceptable	
Alcohol Dose Dumping	Formulation	H	The in vitro release in the presence of alcohol was evaluated and alcohol was found to induce dose dumping in pH 7.2	Acceptable	

			buffer with a concentration of >10% alcohol at the first 1 h time point. Proposed labeling for the Clinical Pharmacology and Clinical Reviewer to consider includes "do not take with alcohol"		
Microbial Limits	Formulation Raw materials Process parameters Scale/equipment Site	L	Microbial limits included in the specification. Microbiological controls found acceptable	Acceptable	
Dissolution	Formulation (coating) Raw Materials	M	The analytical method and results were evaluated. The Applicant revised the dissolution method (b) (4) sequential) and dissolution acceptance criteria per FDA's recommendation.	Acceptable	

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