CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212595Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
NDA: Approval

NDA 212595
Review 1

Drug Name/Dosage Form	Riomet ER, Metformin Hydrochloride for Extended-Release Oral Suspension 100 mg/mL
Strength	Metformin Hydrochloride for Extended-Release Oral Suspension 100 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Ltd

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	11/02/2018
0002	12/19/2018
0008	03/01/2019
0015	05/06/2019
0016	05/15/2019
0022	006/24/2019

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Christopher Galliford	OPQ/ONDP/DNDPII/NDPBVI
Drug Product	Christopher Galliford	OPQ/ONDP/DNDPII/NDPBVI
Process	Ramesh Dandu	OPQ/OPF/DPAII/PABIV
Facility	Ramesh Dandu	OPQ/OPF/DPAII/PABIV
Biopharmaceutics	Sarah Ibrahim	OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Leeza Rahimi	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Christopher Galliford	OPQ/ONDP/DNDPII/NDPBVI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	Sun Plarmaceutical Industries Ltd	Metformin hydrochloride	Adequate		Based on information provided in the NDA
	Type III	(b) (4)				Based on information provided in the NDA
	Type III					Based on information provided in the NDA
	Type III					Based on information provided in the NDA
	Type III					Based on information provided in the NDA
	Type III					Based on information provided in the NDA
	Type III					Based on information provided in the NDA
	Type III					Based on information provided in the NDA

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21591	Riomet

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 212595 is recommended for approval from a CMC perspective. There are no outstanding deficiencies and the manufacturing facilities have an acceptable cGMP recommendation. Labeling comments will be negotiated through the clinical project manager. A 24-month shelf-life will be granted through the approval letter based on stability data at intermediate storage conditions. The product should be stored at room temperature.

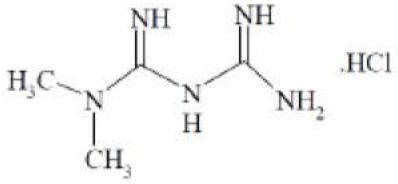
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A.

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The Riomet ER oral suspension is an oral suspension drug product of metformin hydrochloride.



Metformin hydrochloride, 1,1-Dimethylbiguanide hydrochloride, is a white crystalline solid with an absence of polymorphism that is freely soluble in water and slightly soluble in alcohol. Manufacturing, packaging, quality control testing and release. The metformin hydrochloride drug substance is considered satisfactory based on the approved status of NDA 202293.

B. Drug Product [RIOMET ER] Quality Summary

Metformin hydrochloride extended release oral suspension is manufactured to provide a suspension of 100 g per 100 mL. The product is not an NME because the active ingredient is present in previously approved applications. The new product is an oral suspension of metformin HCl as an extended release formulation. There (b) (4) drug product presentations, and in each case the drug product is a combination of a diluent solution and extended release tablets. When these are mixed, the oral suspension is formed, which will be prepared and dispensedby a pharmacist. These presentations are summarized below:

(b) (4)

3) 16 oz. round bottle pack.

At the time of writing, (b) (4) will be approved under this NDA review cycle. The drug product formulation includes common compendial excipients and there are no novel excipients. Three batches are included in the NDA as primary stability batches with a matrix design for container closure systems. All were manufactured at the commercial site using the commercial manufacturing process and scale and packaged in the commercial container closure system. Up to 12-month primary stability data are provided to support a 24-month shelf-life when stored at room temperature. A 24-month expiry is granted. In-use stability of 100 days is granted.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Riomet ER
Non Proprietary Name of the Drug Product	Metformin Hydrochloride for Extended-Release Oral Suspension (b) (4) mg/mL
Non Proprietary Name of the Drug Substance	Metformin Hydrochloride
Proposed Indication(s) including Intended Patient Population	Indicated for use in the treatment of patients with type 2 diabetes mellitus (T2DM)
Duration of Treatment	As directed by physician
Maximum Daily Dose	(b) (4) mg/mL
Alternative Methods of Administration	None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Christopher Galliford -S

Digitally signed by Christopher Galliford -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001708703, cn=Christopher Galliford -S
Date: 2019.07.31 16:32:01 -04'00'

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., 7/30/19

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The sponsor requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (b). To the best of the sponsor's knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action.

Reviewer's Assessment:

The claim for the categorical exclusion is acceptable and the provided information and data are adequate for approval of the NDA application.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:

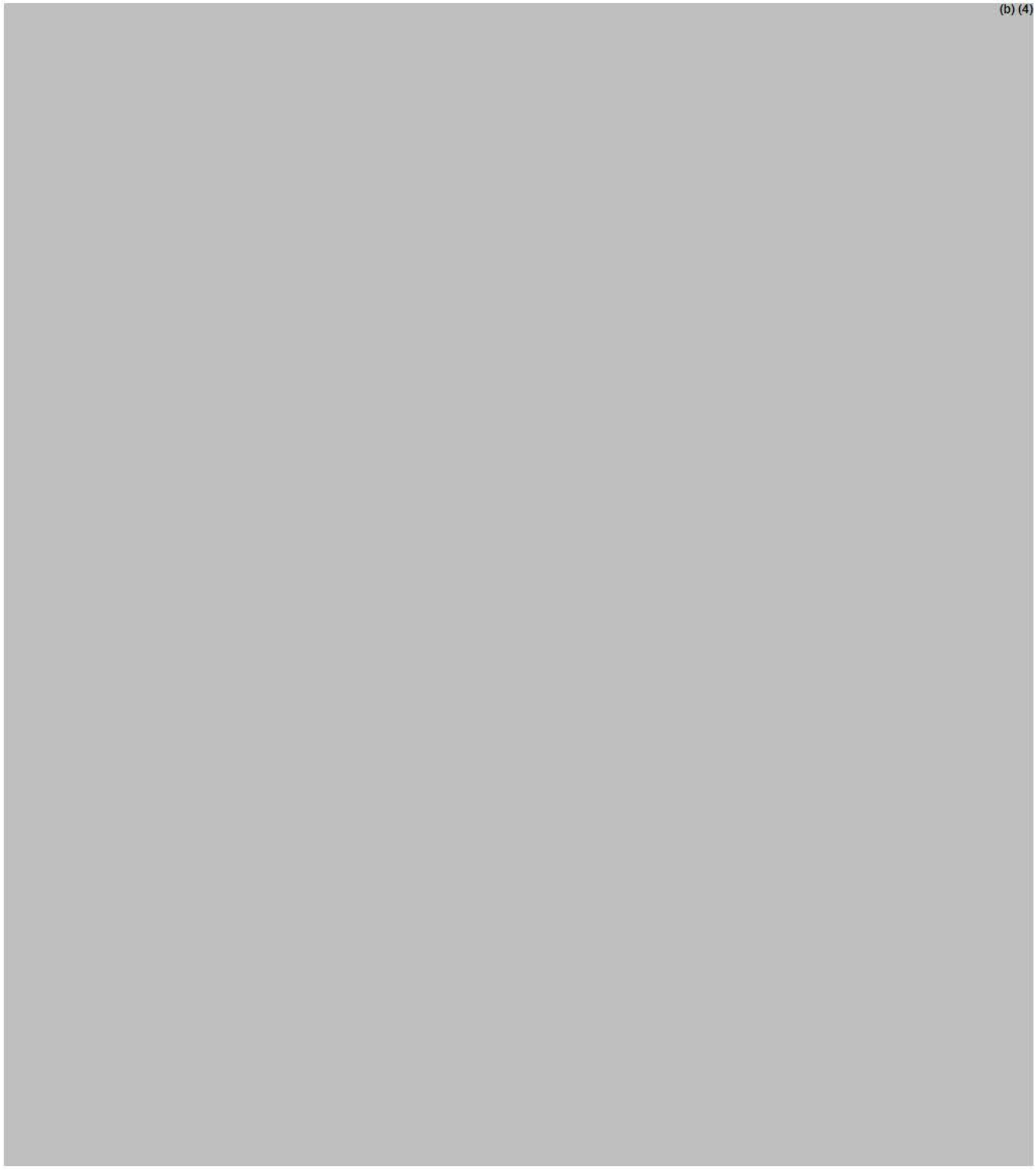
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., 7/30/19

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(b) (4)



(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Riomet ER™ (metformin hydrochloride) extended-release oral suspension, (b) (4)	**Adequate accepted by DMEPA**
Dosage form, route of administration	Suspension for oral administration.	**Adequate**
Controlled drug substance symbol (if applicable)	Not required	**Adequate**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended release suspension (b) (4) mg/mL	**Adequate**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4) extended-release oral suspension, (b) (4) mg/mL

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Extended-release oral suspension (b) (4) mg/mL.	**Adequate**
Strengths: in metric system	(b) (4) mg/mL.	**Adequate**

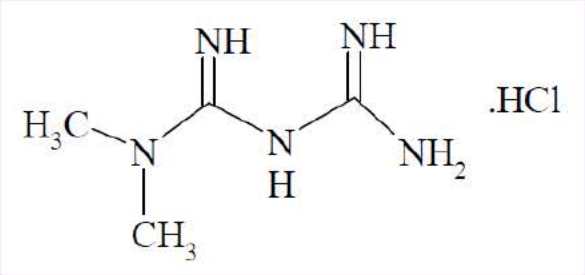
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	RIOMET ER (b) (4) (b) (4) (b) (4) is a biguanide, (b) (4) (b) (4) The chemical name of metformin hydrochloride is *N,N*-dimethylimidodicarbonimidic diamide hydrochloride. The structural formula is as shown below: Metformin hydrochloride, USP is a white crystalline powder with a molecular formula of C4H11N5•HCl and a molecular weight of 165.62. It is freely soluble in water, slightly soluble in alcohol; practically insoluble in acetone and in methylene chloride. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride, USP is 6.37 to 6.53. RIOMET ER is available (b) (4) follow (b) (4): (b) (4) 16 oz. Round Bottle Pack containing white to off-white pellets containing 37.85 g of metformin hydrochloride (equivalent to 29.52 g metformin base) in drug pellets bottle and white to off-white dispersion containing 9.46 g of metformin hydrochloride (equivalent to 7.38	**Adequate**

	g metformin base) in drug diluent bottle intended for reconstitution. Following reconstitution, the volume of the oral suspension is 473.12 mL (16 oz.) containing (b) (4) mg/mL metformin hydrochloride equivalent to (b) (4) mg metformin base. The oral suspension includes the following inactive ingredients: colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, hypromellose, magnesium stearate, methyl paraben, microcrystalline cellulose, microcrystalline cellulose and carboxymethyl cellulose sodium, propyl paraben, sucralose, strawberry flavor Type FL # 28082 (flavoring ingredients, propylene glycol and glycerin) xanthan gum and xylitol.	

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

RIOMET ER (b) (4) is a biguanide, (b) (4). The chemical name of metformin hydrochloride is *N,N*-dimethylimidodicarbonimidic diamide hydrochloride. The structural formula is as shown below:



Metformin hydrochloride, USP is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.62. It is freely soluble in water, slightly soluble in alcohol; practically insoluble in acetone and in methylene chloride. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride, USP is 6.37 to 6.53.

RIOMET ER is available (b) (4) follow (b) (4):

(b) (4)

16 oz. Round Bottle Pack containing white to off-white pellets containing 37.85 g of metformin hydrochloride (equivalent to 29.52 g metformin base) in drug pellets bottle and white to off-white dispersion containing 9.46 g of metformin hydrochloride (equivalent to 7.38 g metformin base) in drug diluent bottle intended for reconstitution. Following reconstitution, the volume of the oral suspension is 473.12 mL (16 oz.) containing (b) (4) mg/mL metformin hydrochloride equivalent to (b) (4) mg metformin base.

The oral suspension includes the following inactive ingredients: colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, hypromellose, magnesium stearate, methyl paraben, microcrystalline cellulose, microcrystalline cellulose and carboxymethyl cellulose sodium, propyl paraben, sucralose, strawberry flavor Type FL # 28082 (flavoring ingredients, propylene glycol and glycerin) xanthan gum and xylitol.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	Adequate
Dosage form and route of administration	Provided	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	Not required	Adequate
Pharmacological/ therapeutic class	Provided	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	Not required	Adequate
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(b) (4):

Store between 20°C to 25°C (68°F to 77°F).
Excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature.]

(b) (4)

The shelf-life of the constituted oral suspension is 100 days. Any unused portion of the reconstituted suspension must be discarded after 100 days.

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(b) (4) mg/mL	Adequate
Available units (e.g., bottles of (b) (4))	RIOMET ER is available (b) (4) follow: (b) (4) [redacted]	Adequate
	16 oz. Round Bottle Pack containing white to off-white pellets containing 37.85 g of metformin hydrochloride (equivalent to 29.52 g metformin base) in drug pellets bottle and white to off-white dispersion containing 9.46 g of metformin hydrochloride (equivalent to 7.38 g metformin base) in drug diluent bottle intended for reconstitution.	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided	Adequate
Storage conditions	Provided	Adequate

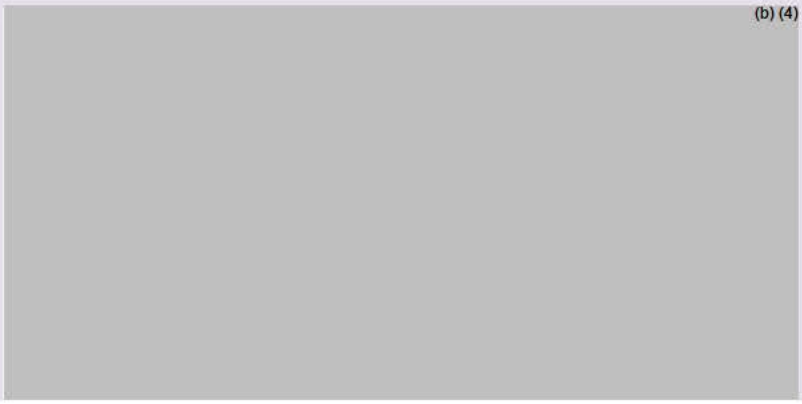
Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: Sun Pharmaceutical Industries Limited MOHALI, INDIA Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512	**Adequate**

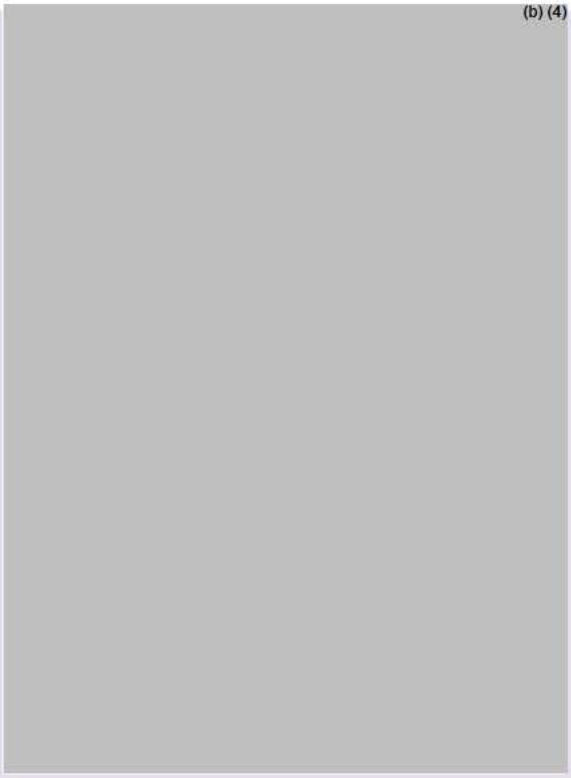
Conclusion: Adequate

2. Container and Carton Labeling

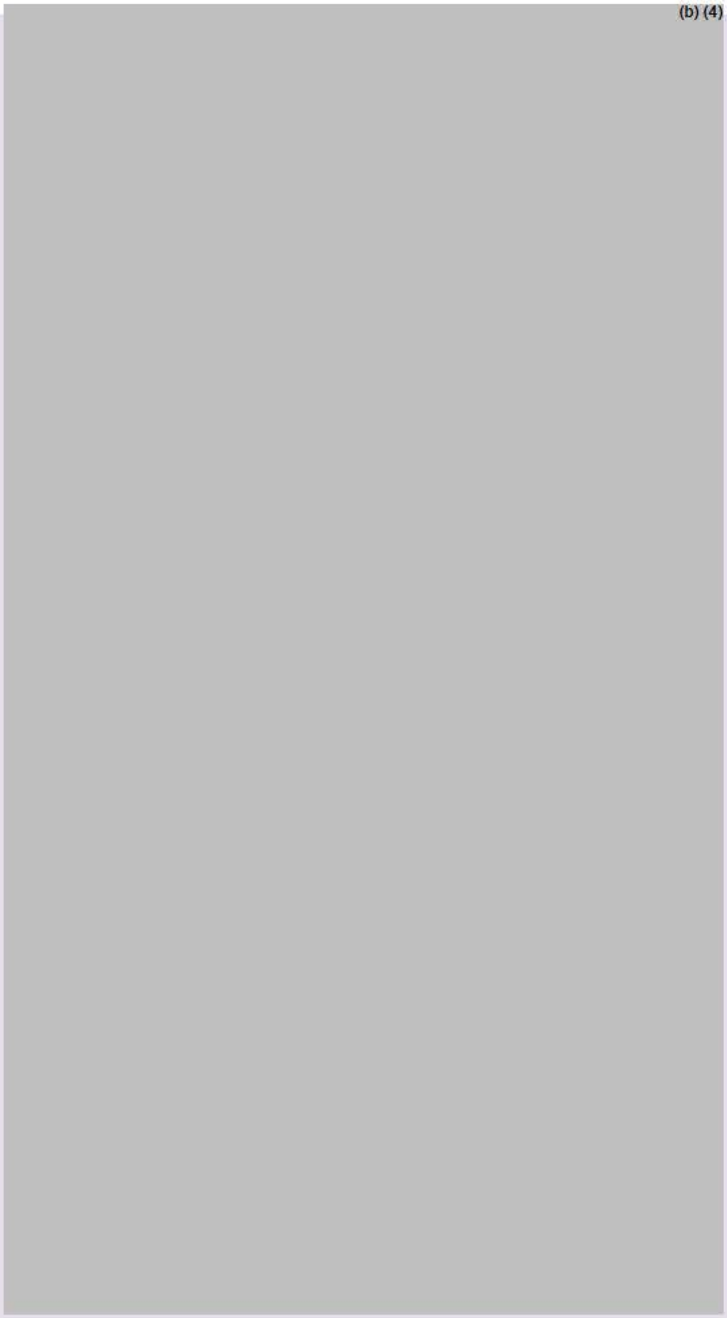
1) Immediate Container Label



(b) (4)



(b) (4)



(b) (4)

Reviewer's Assessment: **The container label is adequate**

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Riomet ER™ (metformin hydrochloride extended-release oral suspension, (b) (4) mg/mL).	**Adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4) mg/mL suspension	**Adequate**
Route of administration 21.CFR 201.100(b)(3))	oral	**Adequate**
Net contents* (21 CFR 201.51(a))	(b) (4) mg/mL	**Adequate**
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided	**Adequate**
Lot number per 21 CFR 201.18	Space is provided	**Adequate**
Expiration date per 21 CFR 201.17	Space is provided	**Adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	**Adequate**
Storage (not required)	Provided	**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	**Adequate**
Bar Code per 21 CFR 201.25(c)(2)***	Provided	**Adequate**
Name of manufacturer/distributor (21 CFR 201.1)	Provided	**Adequate**

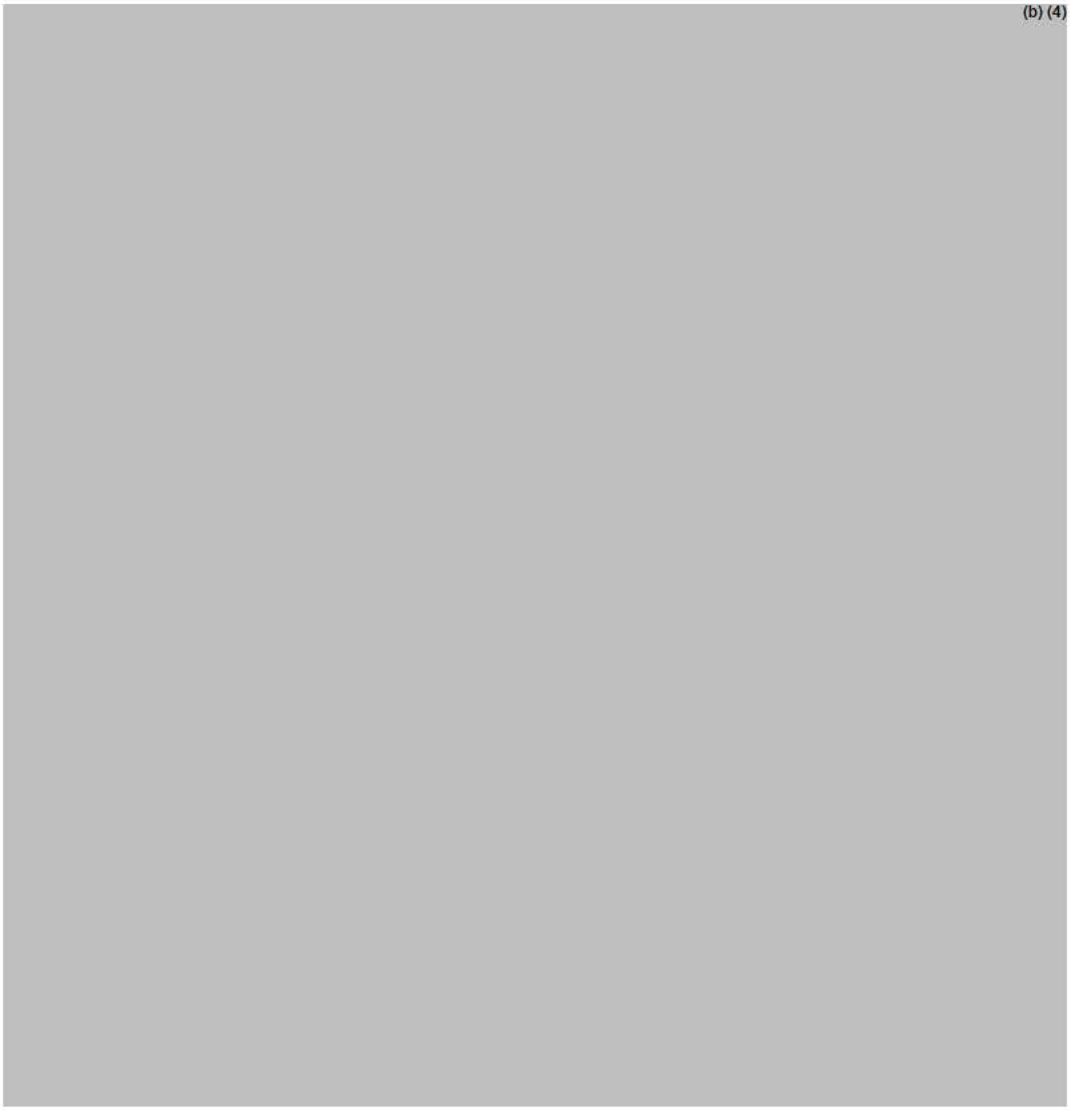
Warnings		(b) (4) (b) (4) Store between 20°C to 25°C (68°F to 77°F) in the original bottle. Excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature.] Do not repackage. The shelf-life of the constituted oral suspension is 100 days. Any unused portion of the reconstituted suspension must be discarded after 100 days. (b) (4)	**Adequate**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

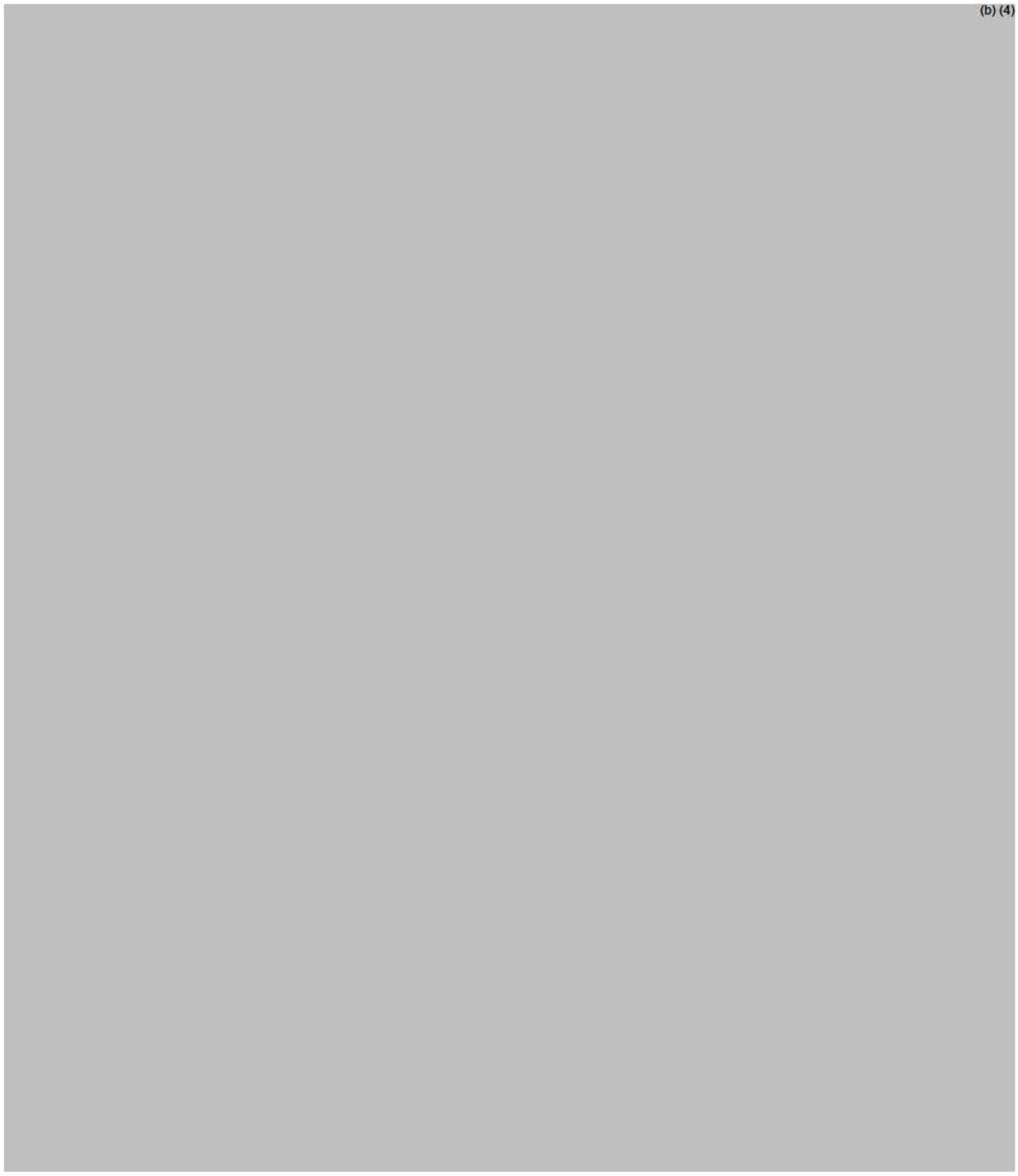
2) Carton Labeling

(b) (4)



(b) (4)

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Riomet ER™ (metformin hydrochloride extended-release oral suspension, (b) (4)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	(b) (4) mg/mL suspension.	Adequate
Net contents (21 CFR 201.51(a))	(b) (4) mg/mL	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Provided	Adequate
Sterility Information (if applicable)	Space is provided	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	(b) (4)	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required	Adequate

Conclusion: Adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

MICROBIOLOGY

Product Background:

NDA/ANDA/BLA: 212595

Drug Product Name / Strength: Metformin Hydrochloride for Extended-Release Oral suspension (b) (4) /mL

Route of Administration: oral

Applicant Name: SUN Pharma

Manufacturing Site: Sun Pharmaceutical Industries Limited (b) (4) Mohali (b) (4), India

Method of Sterilization: Not applicable (non-sterile)

Review Recommendation: The submission **is recommended** for approval on the basis of product quality microbiology.

Review Summary: This is a non-sterile liquid in a two-part container closure system with non-sterile pellets supplied in the top chamber and the diluent (vehicle) supplied in the bottom part of the bottle.

List Submissions being reviewed: 11/02/2018, 05/06/2019 IR response

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: An additional submission dated 12/13/2018 was submitted to the Agency that is not relevant to product quality microbiology.

S Drug Substance – Not applicable

P.1 Description of the Composition of the Drug Product

(Section 3.2.P.1, Description and Composition of the Drug Product.pdf)

- **Description of drug product –** Metformin hydrochloride pellets (b) (4) is non-sterile, non-aqueous

Metformin Hydrochloride immediate release vehicle is a white to off-white liquid non-sterile dispersion (b) (4).

- **Drug product composition –**

(b) (4)

(b) (4)

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BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Metformin Hydrochloride for Extended Release Oral Suspension 100 mg/mL, under the 505(b)(2) path.

NDA: 212595

Drug Product Name / Strength: RIOMET 500 mg/5 mL

Route of Administration: Oral

Applicant Name: Sun Pharmaceuticals Industries Limited.

Review Summary:

Sun Pharmaceutical Industries Limited's (SPIL) Metformin Hydrochloride for Extended-Release Oral Suspension 100 mg/mL, subject of this NDA, is an Extended-Release Oral Suspension formulation with the following description:

1. Metformin Hydrochloride Extended release pellets (b) (4)

2. Metformin Hydrochloride immediate release vehicle (b) (4)

Phase 1: Extended release pellets (b) (4)

Phase 2: The aqueous liquid vehicle (b) (4)

In vitro alcohol interaction studies demonstrate that there is evidence of metformin dose dumping in the presence of alcohol. The concern with alcohol dose dumping is being addressed by the clinical pharmacology team.

The Applicant submitted adequate information to support the extended release designation claim per 21 CFR 320.25(f).

From the Biopharmaceutics perspective, NDA 212595 for is **recommended for approval.**

List Submissions being reviewed (table):

Date of Submission	Purpose of Submission
November 2, 2018	Original
March 18, 2019	S0010
May 15, 2019	S0016
June 10, 2019	S0020

Highlight Key Outstanding Issues from Last Cycle: Applicant was requested to provide additional supporting data and accept the agency's recommended acceptance criteria.

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: N/A for modified release products

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ADEQUATE

Dissolution Method:

The proposed dissolution method is described below:

• Dissolution Media: pH 6.80 phosphate buffer

• Dissolution Media Volume: 1000ml

• Apparatus: USP-II

• RPM: 100

Selection of medium, apparatus, and agitation rate

(b) (4)

(b) (4)

Discriminating ability

- Discriminatory dissolution media studies were carried out in pH 6.80 phosphate buffer, 1000ml, USP II, 100rpm. To understand the impact of manufacturing variables on drug release through the discriminatory nature of the media, a study was carried out to study effect of various levels of % extended release (b) (4). Metformin Hydrochloride extended release pellets phase of reconstituted suspension only contains (b) (4) hence dissolution studies has been carried out on extended release pellet (b) (4).

(b) (4)

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- (b) (4)

- Dissolution profiles for clinical batch is summarized below. The lots used in the registration stability study are also included in the submission and are consistent with the clinical batch.

Test Sample Details	
Test Sample	Metformin Hydrochloride For Extended Release Oral Suspension 100 mg/ml
Batch / Lot No.	2897334
Label Claim	100 mg/ml
Mfg. Date	July/2017
Exp. Date	June/2019
Manufactured By	Sun Pharmaceutical Industries Limited, Mohali, Punjab, India
Market	USA
Date of analysis	29/Sep/2017
Reference No.	MVA17/0446

Dissolution Medium / Appar

Medium Details	Phosphate Buffer pH 6.8	
Temperature	37	°C

Vessel No.	% Drug dissolved / released in test sample												
	30min	1 Hour	2 Hour	3 Hour	4 Hour	12Hour							
1	(b) (4)						NA	NA	NA	NA	NA	NA	NA
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
							NA	NA	NA	NA	NA	NA	NA
Range	(b) (4)						NA	NA	NA	NA	NA	NA	NA
Minimum							NA	NA	NA	NA	NA	NA	NA
Maximum							NA	NA	NA	NA	NA	NA	NA
Mean	19	29	61	78	86	98	NA	NA	NA	NA	NA	NA	NA
Std. Deviation	0.58	0.83	0.72	0.62	0.72	0.79	NA	NA	NA	NA	NA	NA	NA
% CV	3.1	2.9	1.2	0.8	0.8	0.8	NA	NA	NA	NA	NA	NA	NA
Specification Limit	(b) (4)						NA	NA	NA	NA	NA	NA	NA

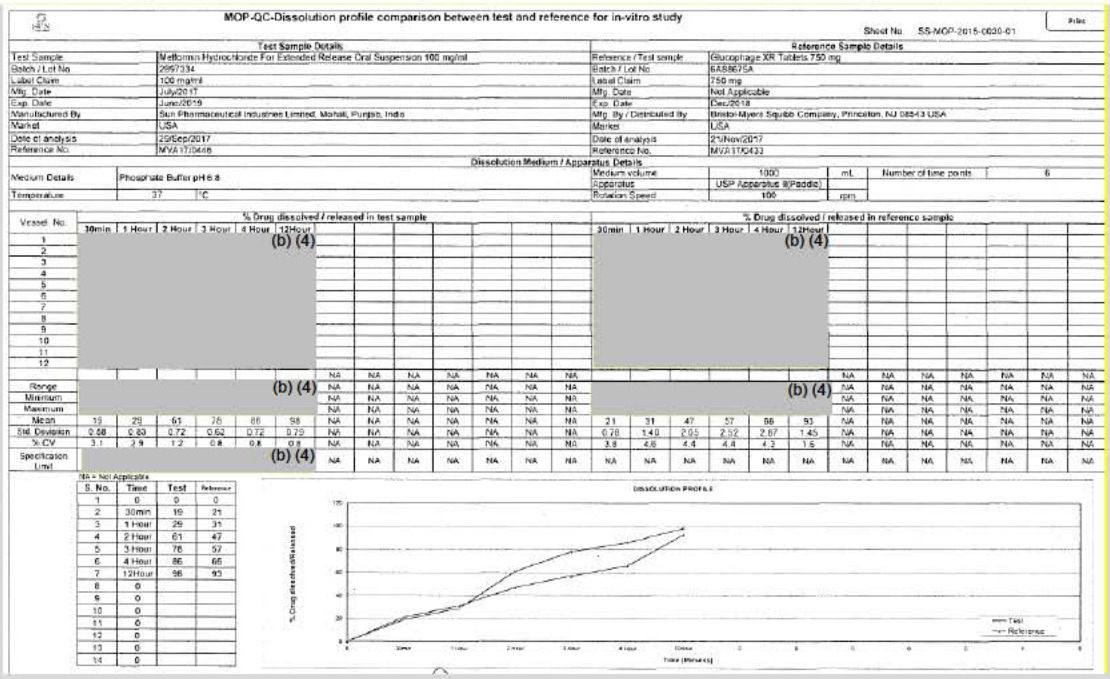
- **The dissolution method is adequate.**

Acceptance Criteria:

- The Applicant proposed the following dissolution acceptance criteria:

0.5 hour: NMT (b) (4)%
2 hours: Between (b) (4)%
(b) (4) hours: NLT (b) (4)%

- The following table and figure summarize the dissolution batch release:



MOP-QC-Dissolution profile comparison between test and reference for in-vitro study

Sheet No SS-MOP-2015-0030-01

Test Sample Details		Reference Sample Details	
Test Sample	Metformin Hydrochloride For Extended Release Oral Suspension 100 mg/ml	Reference / Test sample	Glucophage XR Tablets 750 mg
Batch / Lot No	2897334	Batch / Lot No	6A8867SA
Label Claim	100 mg/ml	Label Claim	750 mg
Mfg. Date	July/2017	Mfg. Date	Not Applicable
Exp. Date	June/2019	Exp. Date	Dec/2018
Manufactured By	Sun Pharmaceutical Industries Limited, Mohali, Punjab, India	Mfg. By / Distributed By	Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Market	USA	Market	USA
Date of analysis	29/Sep/2017	Date of analysis	21/Nov/2017
Reference No.	MVA17/0466	Reference No.	MVA17/0433

Dissolution Medium / Apparatus Details

Medium Details	Phosphate Buffer pH 6.8		Medium volume	1000	mL	Number of time points	6
Temperature	37	°C	Apparatus	USP Apparatus II(Paddle)			
			Rotation Speed	100	rpm		

Vessel No.	% Drug dissolved / released in test sample						% Drug dissolved / released in reference sample					
	30min	1 Hour	2 Hour	3 Hour	4 Hour	12Hour	30min	1 Hour	2 Hour	3 Hour	4 Hour	12Hour
1	(b) (4)						(b) (4)					
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Range	(b) (4)						(b) (4)					
Minimum												
Maximum												
Mean	19	29	61	76	86	98	21	31	47	57	66	93
Std. Deviation	0.58	0.83	0.72	0.62	0.72	0.79	0.78	1.49	2.05	2.52	2.87	1.45
% CV	3.1	2.9	1.2	0.8	0.8	0.8	3.8	4.8	4.4	4.4	4.3	1.6
Specification Limit	(b) (4)											

NA = Not Applicable

S. No.	Time	Test	Reference
1	0	0	0
2	30min	19	21
3	1 Hour	29	31
4	2 Hour	61	47
5	3 Hour	76	57
6	4 Hour	86	66
7	12Hour	98	93
8	0		
9	0		
10	0		
11	0		
12	0		
13	0		
14	0		

- The Applicant submitted mean and range dissolution values for the clinical and registration stability batches, with complete dissolution data (Application 212595 - Sequence 0001 - Comparative Dissolution Profile - Official Media)
- The complete dissolution data does not support the Applicant's proposed dissolution acceptance criteria. Based on the submitted data the acceptance criteria is recommended to be
  0.5 hour: NMT (b) (4)%
  2hours: Between (b) (4)%
  4 hours: NLT (b) (4)%
- An Information Request (IR) was communicated to the Applicant on March 11, 2019 Stating " The complete dissolution data does not support the Applicant's proposed dissolution acceptance criteria. Based on the submitted data the acceptance criteria recommended to be:
  0.5 hour: NMT (b) (4)%
  2 hours: Between (b) (4)%
  4 hours: NLT (b) (4)%"

- The applicant responded to the above-mentioned information request on March 18, 2019 under S0010 and stated that the dissolution profiling at 18 months stability station for batch no. 2897334 and 2890508 and on control samples for batch no 2902272 have been generated on the exhibit batches and the data has been provided and summarized below:

Batch No.	Results at 4 hours (Initial) n=12	Results at 4 hours (18 months Long Term. For 2897334 and 2890508 and Control samples for batch no. 2902272) n=06

2897334 (Bio-batch)	(b) (4)
2890508	
2902272	

- The applicant based on the stability data is requesting the following acceptance criteria:

Present Specifications			*Proposed Specifications*		
Dissolution time points	*Acceptance criteria*		*Dissolution time points*	*Acceptance criteria*	
	Regulatory	*Shelf life*		*Regulatory*	*Shelf Life*
0.5 hr.	NMT (b) (4)%	NMT (b) (4)%	0.5 hr.	NMT (b) (4)%	NMT (b) (4)%
2 hr	(b) (4)%	(b) (4)%	2 hr	(b) (4)%	(b) (4)%
(b) (4) hr	NLT (b) (4)%	NLT (b) (4)%	(b) (4) hr	NLT (b) (4)%	NLT (b) (4)%

- The acceptance criterion for time point 0.5 hours is acceptable and supported by the biobatch release data. The firm's counter-proposed acceptance criteria for time point 2 hours to be (b) (4) (b) (4)% instead of the agency's proposed (b) (4)% is acceptable since the biobatch average release at 2 hours is (b) (4)% and therefore is within acceptable intrinsic variability of the dissolution method. However, the applicant proposed NLT (b) (4)% at (b) (4) hours instead of the agency's proposed 4 hours is not acceptable. The acceptance criteria are based on the release data of the biobatch and not on the stability data, particularly that the biobatch stability data at 18 months that the firm used to justify (b) (4) acceptance criteria conforms and meets the agency's proposed specifications. Therefore, a follow up information request was sent to the applicant on May 9, 2019 proposing the following acceptance criteria:

"Based on the submitted data the acceptance criteria recommended to be:
0.5 hour: NMT (b) (4)%
2 hours: Between (b) (4)%
4 hours: NLT (b) (4)%"

- Under S0016 the firm responded to the agency's May 9, 2019 information request accepting the 0.5 and 2 hour acceptance criteria, however rejecting the 4 hour time point. The firm proposed (b) (4) ours instead of the 4 hours for drug release equivalent to NLT (b) (4)%. The firm is justifying the new proposed specification based on the 18 months stability data for batch numbers 2897334 and 2890508 and on control samples for batch no 2902272 placed at horizontal conditions as shown below

Batch No.	**Results at 4 hours (18 months Long Term. For 2897334 and 2890508 and Control samples for batch no. 2902272) n=06**		
2902272 (b) (4) -upright)		(b) (4)	
2902272 ((b) (4) horizontal)			
2902643 (Round-Horizontal)			

- Metformin has a narrow absorption window making the dissolution release profile critical for the clinical performance of the proposed formulation. The dissolution acceptance criteria is based on the biobatch release profile and not determined by the stability data. More importantly, the dissolution data submitted thus far shows that the average release at 4 hours for all bio and exhibit batches is above (b) (4)% at 4 hours. Due to the narrow absorption window of metformin, and based on the release profile of the biobatch, the agency is proposing NLT (b) (4)% drug release at 4 hours. The applicant can provide justification based on clinical data or any IVIVC data in support of a (b) (4) acceptance criteria. If the applicant fails to provide clinically relevant supportive data, the agency can only rely on the release data of the biobatch and exhibit batches at release and assume that the product release profile is stable through the proposed shelf life and cannot utilize stability data (b) (4) the acceptance criteria in a way that is not supported by clinical data.
- The following information request was sent to the applicant on "The complete dissolution data does not support the Applicant's proposed dissolution acceptance criteria. Based on the submitted data the acceptance criteria are recommended to be:

0.5 hour: NMT (b) (4)%
2 hours: Between (b) (4)%
4 hours: NLT (b) (4)%

We request that you acknowledge your acceptance of the recommended acceptance criteria and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period.

- The applicant accepted the agency's recommendation and revised the dissolution acceptance criteria. Application 212595 - Sequence 0020 - Specifications - FS016899

The dissolution acceptance criteria as of S0020 is acceptable.

Clinical relevance of dissolution method & acceptance criteria (IVIVC)

Reviewer's Assessment: ADEQUATE

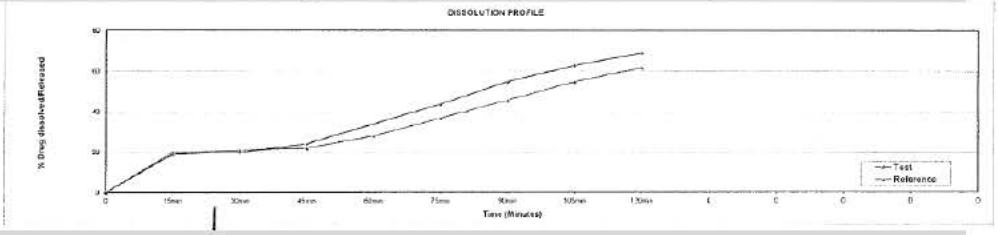
- **Study No.: MFM_100S_0508_17:** Single-dose three-way crossover study to assess the effect of food on bioavailability of Metformin Hydrochloride for extended release oral suspension 100 mg/mL (7.5 mL) and to assess the bioequivalence of Metformin Hydrochloride for extended release oral suspension 100 mg/mL (7.5 mL) (#2897334), manufactured by SPIL, Mohali with Glucophage® XR (Metformin HCl) Extended- Release tablets 750 mg in healthy adult human subjects under fed condition. This study will be reviewed by Clinical Pharmacology Discipline. For additional details please refer to Clinical Pharmacology review.
- No IVIVC model was attempted.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: ADEQUATE

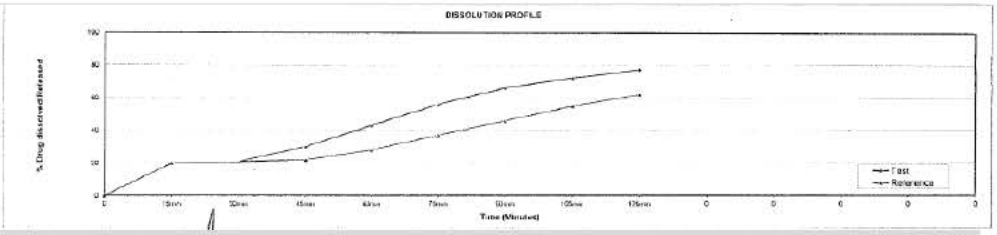
- A study was conducted to evaluate the effect of alcohol on in vitro dissolution of pregabalin ER tablets. Alcohol concentrations of 5%, 20%, and 40% v/v were studied.
- One lot 2897334 was tested using the 0.1 N Hydrochloric Acid + 5, 10, 20 and 40% v/v alcohol.
- Dissolution was tested with n=12 dosage units in each medium. Dissolution samples were collected every 15 minutes for 2 hours.
- The applicant refers to dissolution data using the same dissolution media in the absence of alcohol as a reference under the alcohol dose dumping report.
- An information request was sent on March 18, 2019 to the applicant requesting they provide the complete dissolution profile data (individual, mean, %CV, and profiles) for the alcohol dose dumping study in the absence of alcohol using the same dissolution media for comparison. The response to the information request is addressed below.
- In the presence of 5% alcohol the following is dissolution profile summary

S. No.	Time	Test	Reference
1	0	0	0
2	15min	19	20
3	30min	20	21
4	45min	24	22
5	60min	34	28
6	75min	44	37
7	90min	55	46
8	105min	63	55
9	120min	69	62
10	0		
11	0		
12	0		
13	0		
14	0		



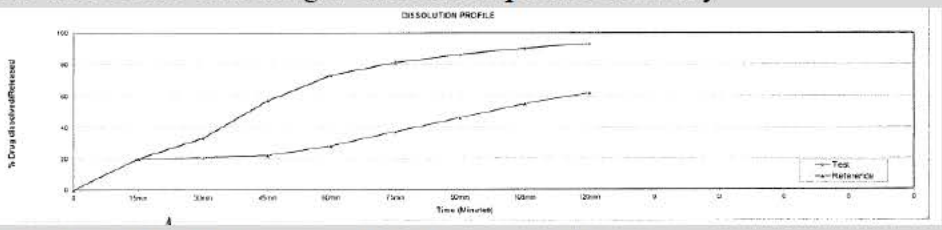
- In the presence of 10% alcohol the following is dissolution profile summary

S. No.	Time	Test	Reference
1	0	0	0
2	15min	20	20
3	30min	21	21
4	45min	30	22
5	60min	43	28
6	75min	56	37
7	90min	66	46
8	105min	72	55
9	120min	77	62
10	0		
11	0		
12	0		
13	0		
14	0		



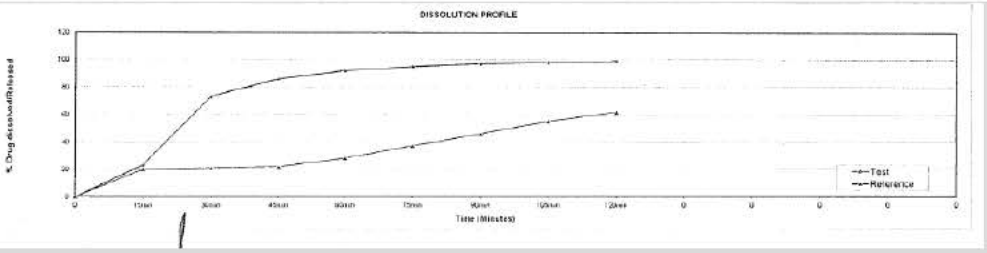
- In the presence of 20% alcohol the following is dissolution profile summary

S. No.	Time	Test	Reference
1	0	0	0
2	15min	20	20
3	30min	33	21
4	45min	57	22
5	60min	73	28
6	75min	81	37
7	90min	88	46
8	105min	90	55
9	120min	93	62
10	0		
11	0		
12	0		
13	0		
14	0		



- In the presence of 40% alcohol the following is dissolution profile summary

S. No.	Time	Test	Reference
1	0	0	0
2	15min	23	20
3	30min	73	21
4	45min	86	22
5	60min	92	28
6	75min	95	37
7	90min	97	46
8	105min	98	55
9	120min	99	62
10	0		
11	0		
12	0		
13	0		
14	0		



- This Reviewer calculated the following f2 calculations per the in vitro alcohol interaction data:

Strength	% EtOH (v/v)	F2
100/1 mg/mL	0% vs. 5%	61
	0% vs. 10%	43
	0% vs. 20%	24
	0% vs. 40%	15

- The f2 values greater than 50 indicate the dissolution profiles with 0% Ethanol are similar to profiles with 5% Ethanol. f2 values for 10, 20 and 40% Ethanol indicate that the dissolution profiles with 0% Ethanol are not similar and the dissolution rate increases with increase in alcohol concentration.
- A clarification information request was sent on March 11, 2019 referencing the alcohol dose dumping study, provide a justification for the four month delay in data calculation and date of analysis. The firm responded the information request stating that the Reviewed dissolution data was available on 16-Feb 2018. Observed dissolution values were further used for F1/ F2 data comparison on 11-Apr-2018. Typographical error was observed in F1/F2 sheet. Hence, these sheets were corrected on 23-Jun-2018. The response to the clarification is Adequate.
- **Therefore, the in vitro alcohol interaction study suggests that there is evidence of alcohol dose dumping.**

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: ADEQUATE

The Applicant submitted the following to support the extended release designation claim per 21 CFR 320.25(f):

1. The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

- Dissolution testing of the drug product using the proposed dissolution method with 0.06 N HCl, and using pH 4.5 acetate buffer and pH 6.8 phosphate buffer, did not show any evidence of in vitro dose dumping. The drug product however did show evidence of in vitro dose dumping in various concentrations of alcohol (see the above ***Dissolution Method and Acceptance Criteria*** section).
- The mean and range of observed Cmax and AUC values summarized below:

Parameter	**Test (B) vs Reference (R)**
C_{max}	106.40 % (102.21 % – 110.75%)
AUC_{0-t}	87.11 % (83.95 % – 90.39 %)
$AUC_{0-\infty}$	86.33 % (83.15 % – 89.64%)

Parameter	Test (B) under fed condition vs Test (A) under fasting condition
C_{max}	79.49 % (74.67% – 84.63%)
AUC_{0-t}	104.56 % (100.56% – 108.73 %)
$AUC_{0-\infty}$	104.56 (100.63% – 108.64%)

- The high-fat meal has resulted in decrease of approximately 20% peak plasma exposure (Cmax).

2. The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.

- Single-dose three-way crossover study to assess the effect of food on bioavailability of Metformin Hydrochloride for extended release oral suspension 100 mg/mL (7.5 mL) and to assess the bioequivalence of Metformin Hydrochloride for extended release oral suspension 100 mg/mL (7.5 mL) with Glucophage® XR (Metformin HCl) Extended-Release tablets 750 mg in healthy adult human subjects under fed condition.

Following oral administration of test product (A -fed or B-fasted) and reference product (R), mean values obtained for pharmacokinetic parameters are as follows:

T_{max} (hr)			C_{max} (ng/mL)			AUC_{0-t} (hr *ng/mL)		
R	A	B	R	A	B	R	A	B
7.4330	4.3654	5.5962	766.48	1067.56	815.39	8932.2920	7472.0207	7694.7811

$AUC_{0-\infty}$ (hr *ng/mL)			Half-life (hr)		
R	A	B	R	A	B
9252.3278	7662.8521	7894.0374	3.9897	4.6352	4.1916

3. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

- No additional data submitted in this application.

4. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

- The proposed will be administered QD (once a day), whereas the approved immediate release oral solution is to be taken twice daily.

The information submitted adequately supports the extended release designation claim per 21 CFR 320.25(f).

Bridging of Formulations

Reviewer's Assessment: N/A

Insufficient information in the application pertaining to the development of the proposed finished product therefore no bridging information was included.

Biowaiver Request

Reviewer's Assessment: N/A

Primary Biopharmaceutics Reviewer Name and Date:
Sarah Ibrahim, Ph.D., January 31, 2019

Sarah Ibrahim, Ph.D., April 1, 2019

Sarah Ibrahim, Ph.D., June 11, 2019

Secondary Reviewer Name and Date:
Haritha Mandula, Ph.D.,

ATTACHMENT I: Final Risk Assessments

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**
Dissolution	Quality of the extended release (b) (4)	H	Continued monitoring of the dissolution according to the revised specification	Acceptable	This CQA is of critical importance to the extended release formulation. The biopharmaceutics reviewer noted several inconsistencies with the analytical method that led to revision of the specification for dissolution.
Particle size distribution	In-use stability of reconstituted suspension depends on tightly controlled PSD throughout the 100 day lifetime of the suspension.	H	Continued monitoring of the PSD according to the tightened PSD specification which should not be relaxed.	Acceptable	Acceptable revised specification. Future batch analysis of PSD results must comply.