CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212516Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: **APPROVAL**

NDA 212516
Review #01

Drug Name/Dosage Form	Duloxetine Delayed Release Capsules
Strength	20 mg, 40 mg, 30 mg, 60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharma Global FZE
US agent, if applicable	Sun Pharmaceutical Industries, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	19-SEP-2018	*Amendment*	07-MAY-2019
Amendment	13-MAR-2019	*Amendment*	20-MAY-2019
Amendment	23-APR-2019	*Amendment*	29-MAY-2019

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Charles Jewell		ONDP
Drug Product	Rao Kambhampati	Wendy Wilson-Lee	
Labeling			
Environmental			
Biopharmaceutics	Zhuojun Zhao	Ta-Chen Wu	
Manufacturing	Zhong Li	Peter Qui	OPF
Microbiology	Jessica Chiaruttini	John Metcalfe	
Regulatory Business Process Manager	Teshara Bouie		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
21752	II	Sun Pharmaceuticals Industries, India	Duloxetine hydrochloride, USP	Adequate	13-JUN-2018	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	131008	Duloxetine Delayed Release Capsules for MDD, GAD, DPNP, FM, and CMP

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 212516.

II. Summary of Quality Assessments

A. Product Overview

Sun Pharma developed a delayed release (DR) capsule formulation of duloxetine for the treatment of major depressive disorder (MDD). This DR capsule formulation is specifically designed to address limitations associated with orally administered duloxetine formulations that must be swallowed. The capsules may be opened to allow sprinkling of the contents over food or administration via nasogastric tubes. The design is intended to improve the patient experience, improve compliance, and reduce medication errors associated with difficulty swallowing. In addition, this formulation offers a new strength – 40 mg – which is currently not marketed under the current duloxetine DR capsule application (ANDA 90745). There are no regulatory designations for this application.

OPQ provided guidance on the qualification of the amount of hypromellose phthalate in the formulation; the proposed drug product specification; the proposed dissolution method; in-use stability requirements; in vitro study requirements to support use in nasogastric, gastronomy, and enteral tubes; proposed commercial batch size; the registration stability protocol; in vitro alcohol dose dumping study design; plans for registration batch manufacturing; and dosage form designation as part of an OND-managed written responses only meeting in 2016. The Applicant identified the following as critical quality attributes for the drug product: bead size, identification, assay, content uniformity, (b) (4) degradants, drug release, (b) (4), microbiological quality, and ability to administer via nasogastric tubes. The initial risk assessment identified solid state, content uniformity, dissolution, bead size, and compatibility with foods and tubes as moderate risk attributes for the product. Alcohol dose dumping was identified as a high-risk attribute for this product. Adequate information was provided in the submission or in response to information requests to mitigate the risks identified such that all attributes are considered low risk at time of regulatory action.

Proposed Indication(s) including Intended Patient Population	*Treatment of Major Depressive Disorder in adults; Generalized Anxiety Disorder in adults and pediatric patients ages 7 years to 17 years old; Diabetic Peripheral Neuropathic Pain in adults; and Chronic Musculoskeletal Pain in adults*
Duration of Treatment	*Chronic*
Maximum Daily Dose	*120 mg*
Alternative Methods of Administration	*Open capsules and sprinkle contents on apple sauce or via nasogastric tube*

B. Quality Assessment Overview

This application references DMF #21752 for the manufacture of the drug substance Duloxetine Hydrochloride, USP. The DMF has been reviewed and the manufacture of the drug substance and its characterization is adequate to support this NDA. Since the drug product manufacturing process (b) (4) (b) (4)

The drug substance is a hydrochloride salt, and there is a USP monograph for the material. The drug substance specifications have limits which meet or provide better quality control than required in the USP monograph. It is a chiral molecule, with a single chiral center and (b) (4) There is one impurity controlled to (b) (4) than the ICH Q3A qualification threshold, limited to NMT (b) (4)% (USP Duloxetine Related Compound F, the dimethyl amine analog of duloxetine), as listed in the USP monograph. However, in batches manufactured by the commercial process listed in this NDA, this impurity is typically well below (b) (4)% w/w. All non-related impurities (i.e., residual solvents, potential mutagenic impurities, and elemental impurities) are controlled by specification or process controls under the DMF.

All methods were described adequately in the application, and the validation reports for each method is included in the application and assessed to be adequate. Method transfer reports are provided for three critical methods that were transferred from the drug substance manufacturing site to the drug product manufacturing site, to provide testing before use in drug product manufacturing. No concerns were noted in assessment of the transfer reports.

The DMF holder claims a retest date, supported by stability study data, of (b) (4) when stored in (b) (4) however the drug product manufacturer has committed to a re-test of the drug substance every (b) (4) from the date of goods receipt to assure acceptability for drug product manufacture. This is acceptable to the FDA.

The proposed components and composition of the DR capsules are adequate. Compatibility of the API with excipients was demonstrated. Amounts of excipients in the capsule were justified by comparing with those in inactive ingredients database except for hypromellose phthalate, however, a prior agreement with the FDA was made. All the excipients are compendial grade or comply with CFR except empty capsule shell, which is made of compendial grade excipients or CFR compliant colorants. Imprinting is also made of compendial grade ingredients. Maximum amount of iron present in the highest dose was justified. Adequate specifications were provided for non-compendial excipients.

The revised specification for the drug product is adequate. Adequate batch analyses results were provided. Adequate justification was provided for the proposed tests in the specification. The analytical methods and their validation reports for the non-compendial methods are adequate. The reference standard and impurity standards are acceptable. The proposed container closure system (HDPE bottles) is commonly used for the packaging of the drug product capsules and adequate data were provided in support of their use. The applicant provided 12 months of stability data for the long-term and intermediate-term and 6 months of data for the accelerated conditions. Given that some out of specification results were observed for some of the accelerated condition samples, the proposed expiration dating period of (b) (4) 18 months when drug product tablet bottles are stored at 20°C - 25°C (68°F - 77°F). The stability protocols and commitments are adequate. The claim for categorical exclusion of environmental assessment is acceptable.

The four strengths of the proposed drug product have the (b) (4)
(b) (4)
(b) (4) Following the review of the applicant's responses to information requests, there is no outstanding manufacturing risk that prevents approval of this application. All facilities are in good standing.

Chemical and physical compatibility of the capsule ingredients with applesauce and nasogastric tube was demonstrated. The proposed administration with food or through a nasogastric tube does not pose any additional microbiological risk above that normally associated with a solid oral dosage form. The capsules are not stored for an extended period in either food or water and as such, there is no potential change to the microbiological quality of the administered dosage form.

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting proposed dissolution method and acceptance criteria, in vitro alcohol dose dumping study as well as waiver requests for the lower strengths. The applicant proposed a two-stage dissolution method: USP Apparatus I (Basket), 100 rpm, Acid-stage 0.1 N HCl with 3.2g of pepsin for 2 hours, Buffer-stage pH 6.8 phosphate buffer, volume 1000 mL at 37oC. The selected dissolution conditions (i.e., apparatus, medium, rotation speed, and addition of pepsin) are adequately justified. The dissolution method was shown to have the ability to detect variations in enteric coating level (i.e., the ability to show failure of acid resistance at (b) (4)% w/w enteric coating level) for the DR capsules. The proposed dissolution method is deemed acceptable base on the totality of the data. Based on the provided dissolution profile data, Division of Biopharmaceutics recommended tightening of acceptance criteria for the Buffer Stage. The applicant agreed to the FDA's recommendation during the review cycle.

The proposed commercial formulation/drug product of 60 mg strength was used in the pivotal relative BA/BE study. There was no manufacturing change to either drug product or drug substance. In addition, all the proposed strengths are proportionally similar in formulation composition and show similar in vitro dissolution profile data. Therefore, additional study for the formulation bridging is not needed.

The applicant provided sufficient supportive information to support the waiver for 20 mg, 30 mg, and 40 mg strengths under 21 CFR 320.22 (d)(2), (i.e., BA/BE study result on the 60 mg bio-batch/bio-strength (batch # 2877521), similar in vitro dissolution profile data for all proposed strengths, proportional similarity of the formulations across all strengths, and same dosage form and release mechanism, and same manufacturing process of lower strengths as the bio-strength 60 mg). The applicant's biowaiver request is granted.

Results of in vitro study suggest a dose-dumping potential of the proposed duloxetine DR Capsules with consumption of alcohol. An in vitro study showed significant increases of duloxetine hydrochloride release from duloxetine delayed release capsules at 2 hours to approximately 86% and 56% of the label claim in the presence of 40% and 20% alcohol, respectively. An effect of 5% alcohol on drug release was not observed at 2 hours. Pertinent labeling recommendations were communicated and implemented in the Section 12.3 Pharmacokinetics of the labeling.

C. Special Product Quality Labeling Recommendations (NDA only)

Recommended language for Prescribing Information Section 12.3 regarding alcohol dose dumping

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Alcohol

An in vitro study showed significant increases of duloxetine hydrochloride release from Drizalma Sprinkle delayed release capsules at 2 hours to approximately 86% and 56% of the label claim in the presence of 40% and 20% alcohol, respectively. Effect of 5% alcohol on drug release was not observed at 2 hours. There is no in vivo study conducted for the effect of alcohol on drug exposure.

LABELING

NDA 212516

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	Drizalma Sprikle™ (duloxetine) Delayed-Release Capsules, USP
Dosage form, route of administration	Delayed-Release Capsules, oral
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes

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)	Yes

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	Capsules containing pellets
Strengths: in metric system	20 mg, 30 mg, 40 mg, and 60 mg
Active moiety expression of strength with equivalence statement (if applicable)	Yes
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

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	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
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>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Yes

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	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

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

The Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container Labels***

Note: In the NDA, bottle labels were provided for 20 mg, 30 mg, 40 mg, and 60 mg strength capsules of 30-count, 60-count, 90-count, and 1000-count bottles. Information for 60 mg capsule bottle labels are provided in this review as a representative example:

30-Count Bottle Label:

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

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	Not applicable
Dosage strength	Yes	Not applicable
Net contents	Yes	Not applicable
"Rx only" displayed prominently on the main panel	Yes	Not applicable
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Not applicable
Lot number and expiration date (21 CFR 201.17)	Yes	Not applicable
Storage conditions	Yes	Not applicable
Bar code (21CFR 201.25)	Yes	Not applicable
Name of manufacturer/distributor	Yes	Not applicable
And others, if space is available	Not applicable	Not applicable

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

The bottle labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies: None

Overall Assessment and Recommendation: From the CMC review stand point the proposed labels are recommended for approval.

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, 5/16/19

Secondary Reviewer Name and Date:

Rao Kambhampati

Digitally signed by Rao Kambhampati
Date: 5/20/2019 04:44:21PM
GUID: 508da72000029fd06e8c9283b7414189

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/21/2019 10:48:46AM
GUID: 50816dbc000085595ca3284bbca465a8

BIOPHARMACEUTICS

Product Background:

NDA: 212516-ORIG-1 [505(b)(2)]

Drug Product Name / Strength: Drizalma Sprinkle (Duloxetine) Delayed Release Capsules, 20, 30, 40 and 60 mg
Route of Administration: Oral

Proposed Indications: Major Depressive Disorder (MDD); Generalized Anxiety Disorder (GAD); Diabetic Peripheral Neuropathy Pain (DPNP); Chronic Musculoskeletal Pain[1]

Applicant Name: Sun Pharma Global FZE

Primary Reviewer: Joan Zhao, Ph.D.

Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY:

Sun Pharma developed Drizalma Sprinkle delayed release (DR) capsule formulation of duloxetine hydrochloride, USP (equivalent to 20 mg, 30 mg, 40 mg and 60 mg of duloxetine free base) for the treatment of major depressive disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Peripheral Neuropathy Pain (DPNP), and Chronic Musculoskeletal Pain. The proposed DR capsule formulation is specifically designed to address limitations associated with orally administered duloxetine formulations that must be swallowed. The proposed Duloxetine DR Capsules 60 mg was assesed in the pivotal relative BA/BE study under fasted, fed and sprinkled with applesauce conditions, compared to the listed drug Cymbalta® (duloxetine) DR Capsules (NDA 021427) under fasted condition.

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting proposed dissolution method and acceptance criteria, in vitro alcohol dose dumping study as well as waiver requests for the lower strengths. Key Biopharmaceutics review findings are summarized below.

In Vitro Dissolution Method and Acceptance Criteria:
The Applicant proposed a two-stage dissolution method: USP Apparatus I (Basket), 100 rpm, Acid-stage 0.1 N HCl with 3.2g of pepsin for 2 hours, Buffer-stage pH 6.8 phosphate buffer, volume 1000 mL at 37ºC. The selected dissolution conditions (i.e., apparatus, medium, rotation speed, and addition of pepsin) are adequately justified. The dissolution method was shown to have the ability to detect variations in enteric coating level (i.e., the ability to show failure of acid resistance at (b) (4)% w/w enteric coating level) for the DR capsules. The proposed dissolution method is deemed acceptable base on the totality of the data.

[1] The proposed indications are in line with Cymbalta® except fibromyalgia due to patent exclusivity concern.

Based on the provided dissolution profile data, Division of Biopharmaceutics recommended tightening of acceptance criteria for the Buffer Stage. The Applicant has agreed to the FDA's recommendation during the review cycle (dated April 26, 2019) as follows:

	Applicant's Proposal	*FDA's Recommendation*
Acid Stage	*NMT (b) (4)% in 2 hours*	*NMT (b) (4)% in 2 hours*
Buffer Stage	*NLT (b) (4)% (Q) at (b) (4) (the time in buffer stage include the time in acid stage)*	*NLT (b) (4)% (Q) at 2 hours and 45 minutes (the time in buffer stage include the time in acid stage)*

Bridging of Formulations:

The proposed commercial formulation/drug product of 60 mg strength was used in the pivotal relative BA/BE study. There was no manufacturing change to either drug product or drug substance. In addition, all the proposed strengths are proportionally similar in formulation composition and show similar in vitro dissolution profile data. Therefore, additional study for the formulation bridging is not needed.

Biowaiver Request:

The Applicant provided sufficient supportive information to support the waiver for 20 mg, 30 mg, and 40 mg strengths under 21 CFR 320.22 (d)(2), (i.e., BA/BE study result on the 60 mg bio-batch/bio-strength (batch # 2877521), similar in vitro dissolution profile data for all proposed strengths, proportional similarity of the formulations across all strengths, and same dosage form and release mechanism, and same manufacturing process of lower strengths as the bio-strength 60 mg). The Applicant's Biowaiver Request is granted.

Alcohol-Induced Dose-Dumping Potential:

Results of in vitro study suggest a dose-dumping potential of the proposed duloxetine DR Capsules with consumption of alcohol. An in vitro study showed significant increases of duloxetine hydrochloride release from Drizalma Sprinkle delayed release capsules at 2 hours to approximately 86% and 56% of the label claim in the presence of 40% and 20% alcohol, respectively. Effect of 5% alcohol on drug release was not observed at 2 hours. Pertinent labeling recommendation has been communicated and implemented in the Section 12.3 Pharmacokinetics of the labeling (see *RECOMMENDATION* below).

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212516 for Drizalma Sprinkle (duloxetine) Delayed Release Capsules, 20, 30, 40 and 60 mg, is recommended for **APPROVAL**. The FDA's approved dissolution method and acceptance criteria are as follows:

Stage	Acid	Buffer
USP Apparatus	USP I (Basket)	
Rotation	100 RPM	
Medium	0.1 N HCl with 3.2 g of pepsin	pH 6.8 Phosphate Buffer
Volume	1000 mL	
Acceptance Criteria	NMT (b) (4)% in 2 hours	NLT (b) (4)% (Q) at 2 hours and 45 minutes

Labeling Recommendation to OND and OCP:

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Alcohol
An in vitro study showed significant increases of duloxetine hydrochloride release from Drizalma Sprinkle delayed release capsules at 2 hours to approximately 86% and 56% of the label claim in the presence of 40% and 20% alcohol, respectively. Effect of 5% alcohol on drug release was not observed at 2 hours. There is no in vivo study conducted for the effect of alcohol on drug exposure.

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission (S0001)	9/19/2018
Information Request Response (S0009)	04/26/2019

I. Drug Substance

The drug substance is reported in crystalline form (b) (4) as well as in amorphous form. (b) (4) is selected by the Applicant to manufacture Duloxetine HCl.

II. BCS Designation: N/A

No official BCS designation request is submitted.

Drug Substance Solubility:

As shown in Table 1, drug substance, Duloxetine HCl, shows pH-dependent aqueous solubility. Results suggest highly soluble drug substance at the proposed highest strength 60 mg (also the maximum dose per day).

Table 1. Solubility of Duloxetine HCL at 37.0°C

Duloxetine Hydrochloride B. No. PNNDLTFL040	
Media	**(Solubility in mg/ml)**
0.1N HCl	3.21
0.01N HCl	89.67
Acetate Buffer(pH 2.8)	159.64
Acetate Buffer (pH 4.5)	73.27
Phosphate Buffer(pH 6.8)	99.21
Phosphate Buffer(pH 7.4)	102.29
Water	63.25

Permeability:

No permeability data is submitted.

III. Formulation:

Duloxetine HCl is an acid labile drug. The proposed duloxetine DR capsule is specifically formulated to address limitations associated with orally administered duloxetine formulations that must be swallowed, as the proposed capsules can be opened to allow sprinkling of the contents over food or administration via nasogastric tubes.

Table 2 summarizes the qualitative and quantitative compositions of the proposed Duloxetine DR capsule. The compositions across strengths are compositionally proportional. The 60 mg strength was used in the pivotal relative BA/BE study.

Table 2. Composition of the Proposed Duloxeine DR Capsules, USP

Ingredients	20 mg	30 mg	40 mg	60 mg	20 mg	30 mg	40 mg	60 mg
	mg / capsule	mg / capsule	mg / capsule	mg / capsule	%w/w	%w/w	%w/w	%w/w
Sugar spheres								(b) (4)
Duloxetine Hydrochloride USP equivalent to Duloxetine[2]	22.4 (b) (4)	33.6 (b) (4)	44.9 (b) (4)	67.3 (b) (4)	20.98	20.98	20.98	20.98
Hypromellose, (b) (4)								(b) (4)
Talc (b) (4)								
(b) (4)								
Hypromellose (b) (4)								
Sucrose (b) (4)								
Talc (b) (4)								
(b) (4)								
Hypromellose Phthalate (b) (4)								
Triethyl Citrate (b) (4)								
Talc (b) (4)								
(b) (4)								
(b) (4)								
Hypromellose (b) (4)								
Titanium Dioxide USP								
Talc (b) (4)								
Polyethylene Glycol (b) (4)								
(b) (4)								
(b) (4)								
Total Fill Weight of pellets[8]								
Empty Gelatin Capsule Shell								

IV. Dissolution Method:

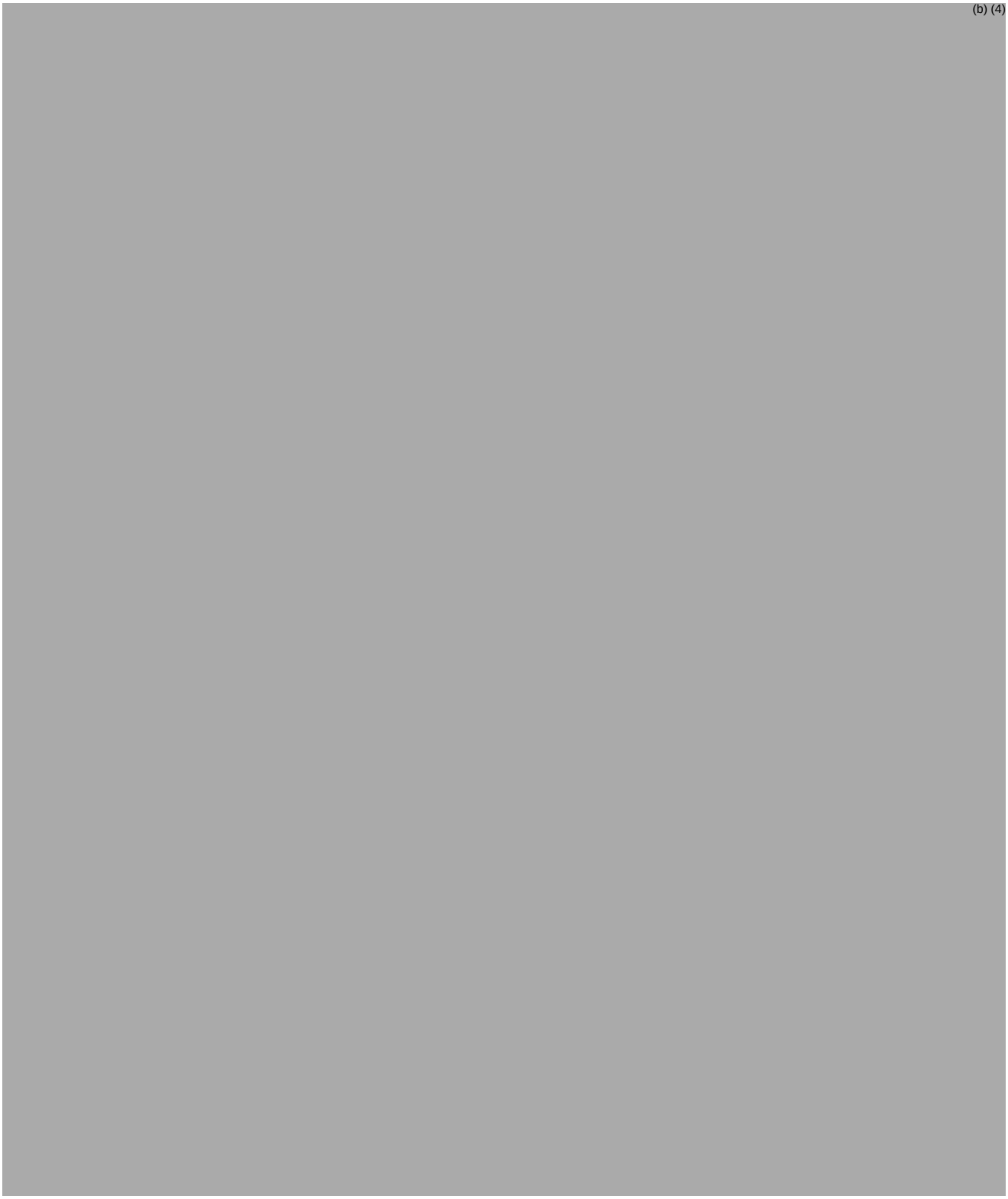
The Applicant initially adopted the (b) (4) dissolution method for the proposed duloxetine DR capsules. However, the Applicant observed slowing of dissolution during testing of stability samples of scale-up batches and exhibit batches. Upon investigation, the Applicant found that the observed slower release was due to cross-linking of capsule shell upon exposure of hard gelatin capsules to accelerated conditions. The (b) (4) method was not capable of (b) (4) .
Hence, the Applicant proposed to use the USP Test 3 method. (b) (4) (***Appendix I***):

Stage	Acid	Buffer
USP Apparatus type	USP I (Basket)	
Rotation	100 RPM	
Medium	0.1 N HCl with 3.2 g of pepsin	pH 6.8 Phosphate Buffer
Volume	1000 mL	

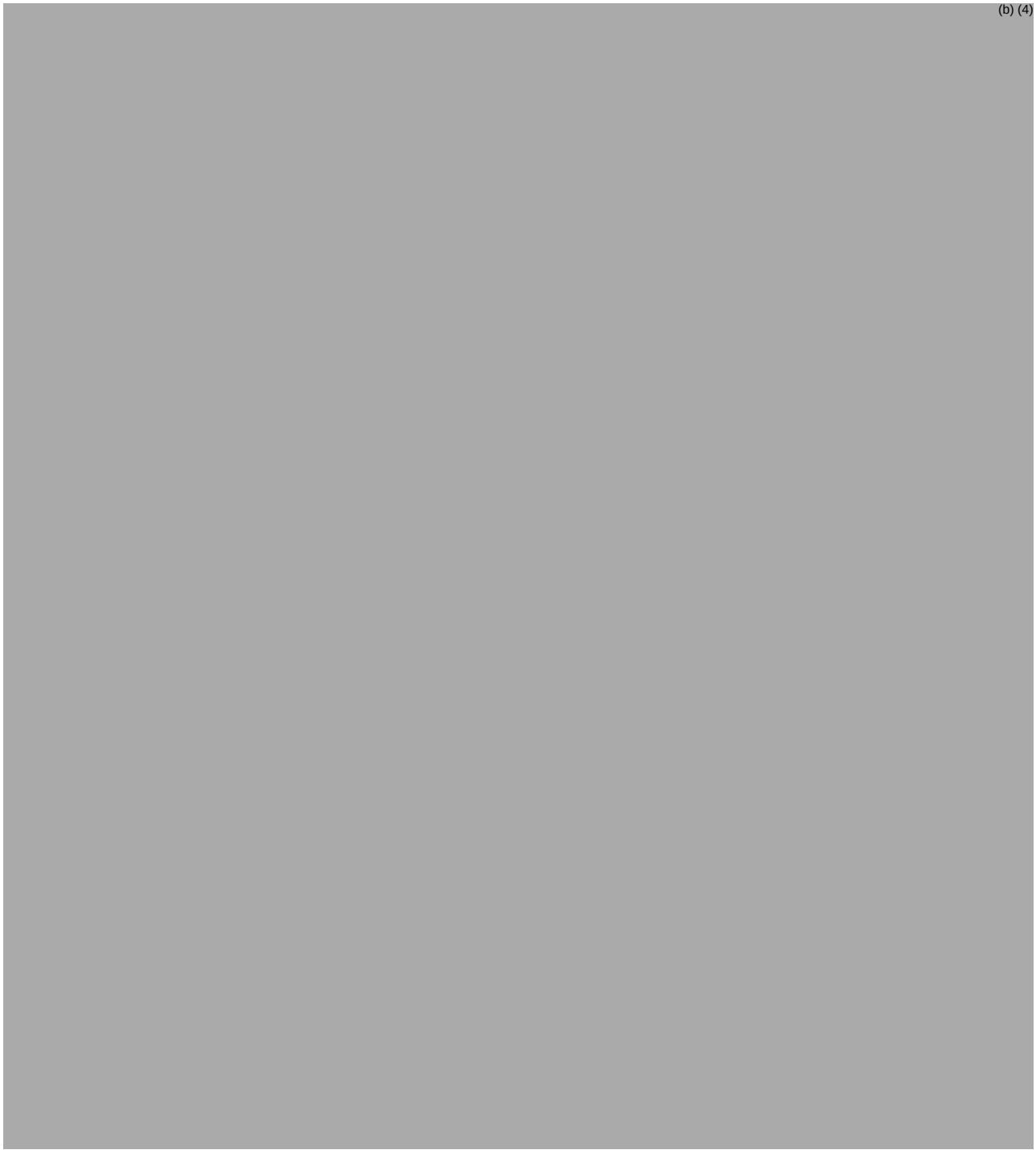
The Applicant provided justifications for the choice of dissolution apparatus, dissolution media, and agitation speed in the Pharmaceutical Development Report, as well as the need for adding pepsin in Addendum 1 of module 3.2.P.2, as detailed below:

(b) (4)

(b) (4)



(b) (4)



(b) (4)

[redacted]

Reviewer's Assessment:

Based on the provided dissolution data and information, the adapted dissolution method, USP Test 3, for Duloxetine DR Capsules, is acceptable for the QC dissolution testing of the proposed DR drug product. The selected dissolution conditions (i.e., apparatus, medium, rotation speed, and addition of pepsin) are adequately justified.

Discriminating Power of the Dissolution Method:

The Applicant evaluated the discriminating power of the proposed dissolution method on the variation of enteric coating levels (target enteric coating at (b) (4)% w/w; see Table 2).

Table 9. Dissolution at % w/w Enteric Coat Weight Build Up

Batch No.	TS(6825)056A	TS(315)001B	TS(315)001C	DDR(316)001
% w/w enteric coat loading (achieved)	[redacted] (b) (4)			
Dissolution (By HPLC) -0.1N HCl 2hr followed by pH 6.80 Phosphate buffer USP I 100 rpm,1000mL				
2hr acid stage	12	0	0	0
15 min	81	76	74	76
30 min	97	85	86	86
45 min	102	90	91	93
60 min	104	91	94	94
90 min	111	96	95	96

Reviewer's Conclusion: Acceptable

Overall, the Applicant has demonstrated the suitability of the dissolution method for batch release and stability testing.

The dissolution method may have limited ability to detect variations in enteric coating level only. Results of the investigation show that the proposed dissolution method has the ability to show failure of acid resistance at [redacted] (b) (4) % w/w enteric coating level, which is deemed acceptable, considering that the product is delayed release capsule.

The proposed dissolution method (i.e., USP Test 3 for Duloxetine DR Capsules) and method validation are found acceptable for the QC of the proposed DR drug product.

Dissolution Acceptance Criteria:

The Applicant proposed the dissolution acceptance criteria as NMT [redacted] (b) (4) % in 2 hours (Acid stage) and NLT [redacted] (b) (4) % (Q) in [redacted] (b) (4) (Buffer stage)[2], which are in line with current USP Test 3 (***Appendix I***).

Based on the provided dissolution profile data as presented in ***Appendix II***, this Reviewer recommended a dissolution acceptance criterion of Q= [redacted] (b) (4) % (Q) at 2 hour and 45 minutes for the buffer stage. The recommended acceptance criterion was conveyed to the Applicant and was agreed upon on during the review cycle, dated April 26, 2019 (see ***Appendix III***).

V. Alcohol Dose Dumping Study:

As agreed in Pre-IND meeting Response[3], the Applicant conducted a comparative in-vitro alcohol-induced dose-dumping study between 0.l N HCI with 0% v/v alcohol (control) and 0.l N HCI with 5%, 20% and 40% on lowest (20 mg) and highest strength (60 mg). Individual dissolution data of Duloxetine, percent of breakdown products [redacted] (b) (4) at each time point, mean values, standard deviations, coefficient of variation (%CV), and plots of the percent release profiles of duloxetine, [redacted] (b) (4) compound over the 2-hour period were provided (***Appendix IV***).

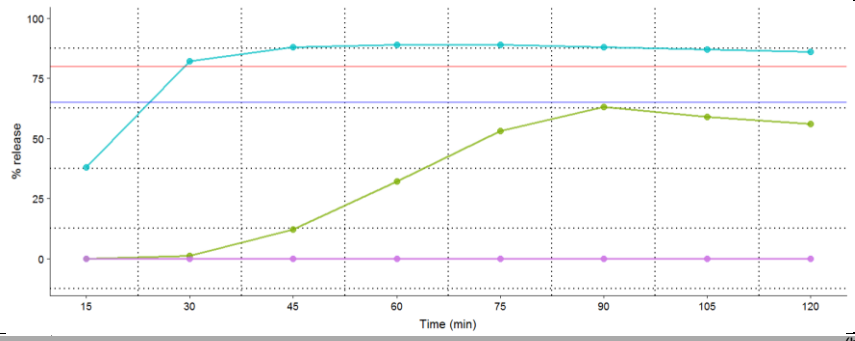
Reviewer's Assessment:

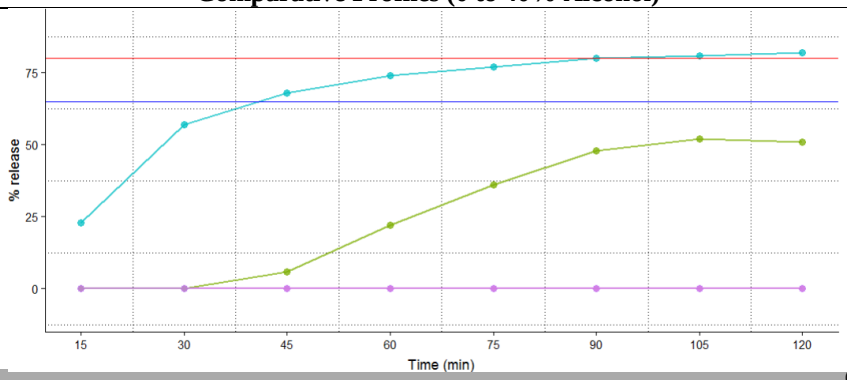
Note that the Applicant conducted the study up to 2 hours only, based on the product-specific Guidance for the generic duloxetine delayed release oral capsule, thus did not

[2] The time in buffer stage medium includes the time in acid stage medium.
[3] DARRTS: IND 131008 COR-MEET-09 (Final Written Response), final date 8/11/2016

provide complete dissolution profiles. The provided results are accepted because of the observed potential dose-dumping within 2 hours already, critical for DR drug products, and the proposed labeling mitigation strategy. The drug release data in the presence of increasing amount of ethanol at 40% and 20% (i.e., 86% and 56% of drug release with 40% and 20% alcohol, respectively) indicate a dose dumping potential of the proposed DR drug product (
Table 10*).*

Table 10. Profiles of the Applicant's Alcohol Dose Dumping Study

Strength	Analyte	Comparative Profiles (0 to 40% Alcohol)
20 mg	Duloxetine	 (b) (4)

Strength	Analyte	Comparative Profiles (0 to 40% Alcohol)
60 mg	Duloxetine	 (b) (4)

Labeling Recommendation:
The Applicant's proposed labeling with Sections highlighted below that are pertinent to results of these studies. Division of Biopharmaceutics provides labeling recommendation specifically to Section 12.3 Pharmacokinetics in track-changes for the OND and OCP.

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Alcohol
An in vitro study showed significant increases of duloxetine hydrochloride release from Drizalma Sprinkle delayed release capsules at 2 hours to approximately 86% and 56% of the label claim in the presence of 40% and 20% alcohol, respectively. Effect of 5% alcohol on drug release was not observed at 2 hours. There is no *in vivo* study conducted for the effect of alcohol on drug exposure.

Reviewer's Comment:

Results of in-vitro study for alcohol-induced dosing dumping potential will be communicated to the Clinical and the Clinical Pharmacology review teams for the proper labeling recommendation.

Pertinent labeling languages were also proposed for Sections 5.2 and 17, and MEDICATION GUIDE (see example below). Note that, as proposed in Section 12.3, concomitant consumption of alcohol is not recommended for all the proposed strengths. However, as proposed, such restriction seems to apply to substantial or heavy alcohol use only as described in Sections 5.2 and 17, and Medication Guide. OND and OCP have been notified.

> **5 WARNINGS AND PRECAUTIONS**
> **5.2 Other Clinically Important Drug Interactions**
> *Alcohol* - Use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, duloxetine delayed-release capsules should not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions (5.2) and Drug Interactions (7.15)]*."

VI. Bridging of Formulations:

The proposed commercial formulation/drug product of 60 mg strength was used in the pivotal relative BA/BE study. No manufacturing changes were made to either drug product or drug substance. Therefore, additional study for the bridging is not needed. Furthermore, all the proposed strengths are proportionally similar in formulation composition and show similar in vitro dissolution profile data (see Section VII Biowaiver Request).

VII. Biowaiver Request:

The Applicant submitted biowaiver request for the lower 20 mg, 30 mg, and 40 mg strengths as per the requirements described in 21 CFR 320.22 (d)(2):

(i) Acceptable BA/BE study results for the 60 mg bio-batch/bio-strength (batch # 2877521),
(ii) Similar in vitro dissolution profiles data for all proposed strengths (see *f*2 table below),

***f*2 Values**	
20 mg (2878714) vs. 60 mg (2877521)	85.65
20 mg (2878711) vs. 60 mg (2877521)	57.42
20 mg (2878712) vs. 60 mg (2877521)	64.22
30 mg vs. 60 mg (2877521)	78.49
40 mg vs. 60 mg (2877521)	75.85

(iii) Proportional similarity of the formulations across all strengths (Table 2),
(iv) Same dosage form and release mechanism, and same manufacturing process of lower strengths as the bio-strength 60 mg,
(v) Dose-proportionality/linearity over the therapeutic range.

The Applicant's biowaiver request is granted.

APPENDIX III: Biopharmaceutics Information Request Dated April 17, 2019 and the Applicant's Response on April 26, 2019

Biopharmaceutics Information Request Comments:

Based on the dissolution data provided for your proposed Duloxetine DR Capsules, 20, 30, 40 and 60 mg, *FDA recommends the following dissolution buffer stage acceptance criteria:*

Acid Stage	*NMT (b) (4)% in 2 hours*
Buffer Stage	*Q (b) (4)% at 2 hours and 45 minutes (the time in buffer stage include the time in acid stage)*

Be aware that setting of the dissolution acceptance criterion are based on level 2 testing (n=12) and therefore sometimes level 2 testing and occasional level 3 testing maybe needed. Revise the finished product QC specifications and other pertinent NDA documents accordingly.

Applicant's Response to Biopharmaceutics IR Comment:

Response: As per Agency's recommendations, Sun Pharma Global FZE has tightened the dissolution limits at buffer stage as mentioned in below table-1:

Table-1: Current and proposed limits for Dissolution

Test	Current Release/Stability	Proposed Release/Stability
Dissolution (By HPLC)		
Acid Stage	NMT (b) (4)% in 2 hours	No change i.e. NMT (b) (4)% in 2 hours
Buffer Stage	NLT (b) (4)% (Q) at (b) (4) (the time in buffer stage include the time in acid stage	**NLT (b) (4)% (Q) at 2 hours and 45 minutes@ (the time in buffer stage include the time in acid stage**

Further, following note has been captured under the test for dissolution in finished product specification due to tightening of dissolution limit at buffer stage w.r.t. limits mentioned in USP monograph.

USP dissolution test pending as the Dissolution Test is different from the current USP monograph.

Additionally, Sun Pharma Global FZE confirms that inline with the revised dissolution limits, statement '(b) (4) would be added in place of '(b) (4) in **section 11 DESCRIPTION** of the proposed package insert labeling and submit it to FDA in response to information request (email dated April 08, 2019).

Reviewer Assessment: The Applicant's response is satisfactory.

APPENDIX IV: Alcohol Dose Dumping Study

Duloxetine:

Dissolution Conditions	**Apparatus:**	USP Apparatus I (Basket) (Duloxetine)										
	Speed of Rotation:	100 rpm										
	Medium:	0.1N Hydrochloric acid + 0%, 5 %, 20% and 40% (v/v) alcohol										
	Volume:	1000 ml										
	Temperature:	37 °C										
Dissolution Testing Site (Name, Address)	Sun Pharmaceutical Industries Limited, A-41, Mohali, Punjab (India)											
Testing Date	**Product ID \ Batch No. (Test - Manufacture Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							
					15min	**30min**	**45min**	**60min**	**75min**	**90min**	**105min**	**120min**
23-Dec-2017	Duloxetine DR Capsules, 20 mg [Batch. /Lot No.2878714] Manufacturing Date: May/2017 Expiry Date: April/2019	20 mg Capsules (0% alcohol)	12	Mean	0	0	0	0	0	0	0	0
				Range	00	00	00	00	00	00	00	00
				%CV	NA	NA	NA	NA	NA	NA	NA	NA
28-Dec-2017	Duloxetine DR Capsules, 20 mg [Batch. /Lot No.2878714], Manufacturing Date: May/2017 Expiry Date: April/2019	20 mg Capsules (5 % Alcohol)	12	Mean	0	0	0	0	0	0	0	0
				Range	00	00	00	00	00	00	00	00
				%CV	NA	NA	NA	NA	NA	NA	NA	NA
29-Dec-2017	Duloxetine DR Capsules, 20 mg [Batch. /Lot No.2878714], Manufacturing Date: May/2017 Expiry Date: April/2019	20 mg Capsules (20 % Alcohol)	12	Mean	0	1	12	32	53	63	59	56
				Range	00	0-1	10-14	30-34	50-56	59-67	54-62	53-60
				%CV	NA	104.4	11.6	5.2	3.9	3.7	3.5	3.7
21-Dec-2017	Duloxetine DR Capsules, 20 mg [Batch. /Lot No.2878714], Manufacturing Date: May/2017 Expiry Date: April/2019	20 mg Capsules (40 % Alcohol)	12	Mean	38	82	88	89	89	88	87	86
				Range	30-44	78-85	83-91	84-93	84-93	83-93	81-92	80-91
				%CV	9.9	2.5	3.0	3.2	3.4	3.8	4.0	4.3

Dissolution Conditions	**Apparatus:**	USP Apparatus I (Basket) (Duloxetine)
	Speed of Rotation:	100 rpm
	Medium:	0.1N Hydrochloric acid + 0%, 5 %, 20% and 40% (v/v) alcohol
	Volume:	1000 ml
	Temperature:	37 °C
Dissolution Testing Site (Name, Address)	Sun Pharmaceutical Industries Limited, A-41, Mohali, Punjab (India)	

Testing Date	**Product ID \ Batch No. (Test - Manufacture Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							
					15min	**30min**	**45min**	**60min**	**75min**	**90min**	**105min**	**120min**
27-Dec-2017	Duloxetine DR Capsules, 60 mg [Batch. /Lot No.2877521] Manufacturing Date: May/2017 Expiry Date: April/2019	60 mg Capsules (0 % Alcohol)	12	Mean	0	0	0	0	0	0	0	0
				Range	00	00	00	00	00	00	00	00
				%CV	NA	NA	NA	NA	NA	NA	NA	NA
27-Dec-2017	Duloxetine DR Capsules, 60 mg [Batch. /Lot No.2877521], Manufacturing Date: May/2017 Expiry Date: April/2019	60 mg Capsules (5 % Alcohol)	12	Mean	0	0	0	0	0	0	0	0
				Range	00	00	00	00	00	00	00	00
				%CV	NA	NA	NA	NA	NA	NA	NA	NA
01-Jan-2018	Duloxetine DR Capsules, 60 mg [Batch. /Lot No.2877521], Manufacturing Date: May/2017 Expiry Date: April/2019	60 mg Capsules (20 % Alcohol)	12	Mean	0	0	6	22	36	48	52	51
				Range	00	00	2-11	16-28	27-47	34-58	39-58	40-59
				%CV	NA	NA	62.3	20.2	19.7	17.4	14.3	12.9
01-Jan-2018	Duloxetine DR Capsules, 60 mg [Batch. /Lot No.2877521], Manufacturing Date: May/2017 Expiry Date: April/2019	60 mg Capsules (40 % Alcohol)	12	Mean	23	57	68	74	77	80	81	82
				Range	5-35	26-70	39-79	48-83	55-85	60-87	65-88	70-88
				%CV	51.0	24.4	18.3	15.1	12.7	11.1	9.1	7.6

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Zhuojun Zhao

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