CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204516Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS NDA REVIEW AMENDMENT Office of New Drug Quality Assessment			
Application No.:	NDA 204-516		
Submission Date:	8-MAY-2013 (Amendment)	**Reviewer:** Deepika Arora Lakhani, PhD	
Division:	Division of Reproductive and Urologic Drug Products	**Biopharmaceutics Team Leader (acting):** Sandra Suarez Sharp, PhD	
Sponsor:	Noven Therapeutics	**Biopharmaceutics Supervisor (Acting):** Richard Lostritto, PhD	
Trade Name:	(b) (4) (Proposed)	**Date Assigned:**	Oct 15, 2012
Generic Name:	Paroxetine Mesylate	**Date of Review:**	May 24, 2013
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause	**Type of Submission:** New Drug Application 505b(2)	
Formulation/ strengths	Capsules, 7.5 mg		
Route of Administration	Oral		

SUMMARY:

The NDA submission is a 505(b)(2) application for Paroxetine mesylate, a selective serotonin reuptake inhibitor, that was previously approved as 10, 20, 30, and 40 mg paroxetine (as mesylate) tablets (PEXEVA® [paroxetine {as mesylate}] tablets) under NDA 21-299. The Applicant for the current NDA and for the approved Pexeva® tablets is the same (Noven Therapeutics). (b) (4)

PENDING ISSUES:

The Biopharmaceutics review for this NDA was completed on 26-APR-2013 with a pending recommendation for the dissolution acceptance criterion. This amendment addresses the pending dissolution acceptance criterion issues.

During a teleconference dated April 25, 2013 the Applicant was advised, based on the provided mean dissolution data from clinical and stability batches, to (b) (4) the dissolution acceptance criterion from Q= (b) (4) to Q= (b) (4) at 20 min. The Applicant responded on 8-MAY-2013 agreeing to the recommended acceptance criterion of Q= (b) (4) at 20 mins.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed the amendment submitted on 8-MAY-2013. The following dissolution method for paroxetine mesylate capsules is deemed acceptable:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
Paroxetine Mesylate	Capsule	II (paddle) with wire	75	simulated gastric fluid (pH 1.20 ±	900 mL

The following dissolution acceptance criterion has been recommended for paroxetine mesylate capsules and accepted by the Applicant:

Q=(b) (4) at 20 minutes

From the Biopharmaceutics perspective, NDA 204-516 for (b) (4) (paroxetine mesylate) Capsules is recommended for APPROVAL.

Deepika Arora Lakhani, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, PhD
Biopharmaceutics Team Leader (acting)
Office of New Drug Quality Assessment

cc. *on file; RLostritto, ADorantes*

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/s/

DEEPIKA LAKHANI
05/24/2013
Recommend Approval from Biopharmaceutics perspective.

SANDRA SUAREZ
05/24/2013

Clinical Pharmacology Review	
NDA Number:	204516
Submission Dates:	08/28/12, 12/12/12, 04/26/13, 05/08/13
Brand Name:	Brisdelle™
Generic Name:	Paroxetine mesylate
OCP Reviewer:	Li Li, Ph.D
OCP Team Leader:	Myong Jin Kim, Pharm.D
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Bone, Reproductive and Urologic Products
Sponsor:	Noven Therapeutics, Inc.
Submission Type:	Original
Formulation; strength:	Capsule; 7.5 mg
Indication:	Treatment of moderate to severe vasomotor symptoms associated with menopause

An optional Inter-Division Clinical Pharmacology Briefing was held on February 25, 2013. The attendees were as follows: Edward D. Bashaw, Myong-Jin Kim, Lisa Soule, Ronald Orleans, Gilbert Burckart, LaiMing Lee, Chongwoo Yu, Hyunjin Kim, Sayed Al Habet, Preveen Balimane, Na Hyung Kim and Hyewon Kim.

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Executive Summary

The Sponsor submitted a New Drug Application (NDA) under 505 (b)(2) for paroxetine mesylate 7.5 mg capsules on August 28, 2012 to seek approval for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Higher doses (10 to 60 mg) of paroxetine are approved for psychiatric indications since 1992. Specifically, Paxil® tablets containing paroxetine hydrochloride salt were approved for the treatment of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and post-traumatic stress disorder on December 29, 1992 (NDA 020031). Subsequently, Pexeva® tablets containing paroxetine mesylate salt were approved for the same indications as Paxil on July 3, 2003 (NDA 021299). For the current submission (NDA 204516), the Sponsor has cross-referenced NDA 020031 (Paxil®), their own NDA 021299 (Pexeva®) and IND 76636. From the clinical pharmacology perspective, the Sponsor conducted one pharmacokinetic (PK) study to establish paroxetine PK profiles after single and repeated doses of paroxetine 7.5 mg in the target population of postmenopausal women (Study N30-005). In addition, the

Sponsor conducted a Phase II proof-of-concept study and two Phase III studies (Study N30-003 and N30-004) to establish the safety and efficacy of paroxetine 7.5 mg for the VMS treatment.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 204516 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert.

- **Phase IV Commitment/Requirement**

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Drug Product Formulation

Brisdelle™ (paroxetine 7.5 mg) is an immediate release (IR) capsule. It contains 9.69 mg of paroxetine mesylate (equivalent to 7.5 mg of paroxetine base) filled in a Size 3 hard gelatin capsule. (b) (4)

[redacted]

Absorption, Distribution, Metabolism, and Excretion (ADME)

The Sponsor determined paroxetine PK profiles after single and repeated oral doses of paroxetine 7.5 mg. No other specific studies describing the ADME of paroxetine 7.5 mg were conducted. The Sponsor is proposing to use the information from the Paxil® and Pexeva® for their product. The PK properties of paroxetine are summarized in **Table 1**.

Table 1 Important PK properties of paroxetine

PK Property	PK Parameter	
Absorption	Bioavailability (F)	~ 50%
	T_{max} (hour)	~ 6 hours*
	Food Effect	Absorption is not affected by food
	Accumulation Index	10-fold*
Distribution	Volume of distribution	Extensive distribution to tissues with only 1% in systemic circulation
	Protein binding	95%
	Pathways	Extensively metabolized after oral administration The metabolism of paroxetine is accomplished in part by cytochrome CYP2D6
Metabolism	Active metabolites	None
	$T_{1/2}$ (hour)	~ 17 hour*
Excretion	Renal	64% excreted in the urine with less than 2% as parent compound
	Fecal	36% excreted in the feces with less than 1% as parent compound

*: Information obtained from Study N30-005.

Drug-Drug Interactions:

No new DDI studies were conducted for paroxetine 7.5 mg. The Sponsor is proposing to use the

information from Paxil® and Pexeva® for their product:

- PK- based DDI: Effect of other drugs on paroxetine:

Concomitant use of paroxetine with other drugs that alter CYP enzymes activities including CYP2D6 may affect the plasma concentrations of paroxetine.

- PK- based DDI: Effect of paroxetine on other drugs

Paroxetine causes irreversible auto-inhibition of CYP2D6 by formation of a metabolite inhibitory complex with the heme iron. Concomitant use of paroxetine with other drugs metabolized by CYP2D6 may lead to a substantially increased systemic exposure of these drugs and may require lower doses than usually prescribed (See detailed information in Section 2.4.1).

- Other interactions

Paroxetine is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of discontinuing treatment with an MAOI. Caution is advised when paroxetine is taken with serotonergic drugs, drugs that interfere with hemostasis, central nervous system (CNS) active agents and drugs highly bound to plasma proteins (See detailed information in section 2.4.1).

Specific Populations:

- Renal or Hepatic Impairment: Based on the information from Paxil® label, paroxetine exposure ($AUC_{0\text{-}inf}$) in patients with creatinine clearance (CrCl) below 30 mL/min were approximately 4 times greater than those in healthy volunteers with normal renal function. Patients with CrCl of 30 to 60 mL/min and patients with hepatic impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}). Dose adjustment is not necessary considering that the current dose (7.5 mg/day) is lower than 10 mg/day, the recommended initial dose of Paxil® or Pexeva® for patients with severe renal or hepatic impairment for the approved psychiatric indications.

- Geriatric Use: Clinical studies of paroxetine 7.5 mg did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients. In particular, the elderly subjects (≥65 years) only represented 6.5% of study subjects in the pivotal Phase III studies of paroxetine 7.5 mg.

  Based on the information from Paxil® label, the minimum plasma (C_{min}) concentrations in elderly subjects were about 70% to 80% higher than the respective C_{min} in nonelderly subjects. Nonetheless, dose adjustment is not considered necessary for elderly patients considering the low dose (7.5 mg) relative to approved paroxetine doses (10 - 60 mg) for the psychiatric indications.

- Body Mass Index (BMI): The Sponsor conducted a subgroup analysis to assess the effect of BMI on paroxetine efficacy for VMS treatment. The analysis data suggested that BMI might affect the treatment outcome of paroxetine. In particular, the mean weekly reduction in the frequency of moderate to severe hot flashes from Baseline to Week 12 (Study N30-003) or to Week 24 (Study N30-004) was significantly greater for the paroxetine group than for the placebo group in the BMI <32 kg/m^2 subgroup but not in the BMI ≥ 32 kg/m^2 subgroup. However, per Statistic reviewer, Dr. Jia Guo, the sub-group analysis may not have enough statistic power and should be treated as exploratory analysis.

Bioanalytical Method:

Blood samples were collected for the determination of paroxetine in plasma using a validated liquid chromatographic tandem mass spectrophotometric method (LC/MS/MS). Acceptance criteria and assay performance for paroxetine were found to be acceptable.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the Clinical Pharmacology and Biopharmaceutics of this drug?

This is a 505(b)(2) submission for the new indication, new dosage form, and new strength for paroxetine. Paroxetine hydrochloride salt tablets were approved on December 29, 1992 under the trade name Paxil® (GSK, NDA 020031), which is indicated for major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and post-traumatic stress disorder. Subsequently, Pexeva® tablets containing paroxetine mesylate salt were approved on July 3, 2003 (Noven, NDA 021299) for the indication of major depressive disorder, obsessive compulsive disorder, panic disorder and generalized anxiety disorder. Both products are available in four strengths, 10, 20, 30, and 40 mg IR tablets. In addition, Paxil® controlled release (CR) 12.5, 25, and 37.5 mg tablets were approved on February 16, 1999 (NDA 020936). The dose and dosing regimen vary by indications and range from 10 mg/day to a maximum of 60 mg/day.

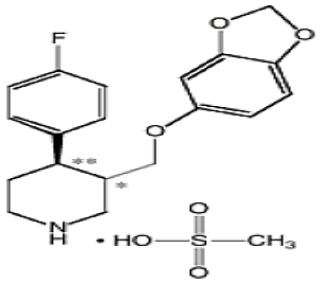
It should be noted that Pexeva® was approved as a 505(b)(2) submission, and thus the clinical pharmacology information was mainly adopted from the Paxil® label. For the current submission, the Sponsor has cross-referenced NDA 020031 (Paxil®), their own NDA 021299 (Pexeva®) and IND 76636.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Active substance:

The active pharmacologic ingredient in Brisdelle™ is paroxetine mesylate. Paroxetine mesylate is an odorless, off-white powder chemically described as (-)-trans -4R- (4'-fluorophenyl) - 3S - [(3', 4'-methylenedioxyphenoxy) methyl] piperidine mesylate. It has the empirical formula of $C_{19}H_{20}FNO_3 \bullet CH_3SO_3H$. The molecular weight is 425.5 (329.4 as free base). The structural formula is shown in **Figure 1.**

Figure 1 Paroxetine mesylate chemical structure



Formulation:

This is an IR capsule. It contains 9.69 mg of paroxetine mesylate (equivalent to 7.5 mg of paroxetine base) filled in a Size 3 hard gelatin capsule. The composition of and function of each components of the capsule are shown in **Table 2.**

Table 2 Composition of paroxetine mesylate capsules, 7.5 mg

Component	Reference to Quality Standards	Function	% w/w	mg/capsule
Paroxetine Mesylate	In-house (NDA 021299)	Drug substance	(b) (4)	9.69[a,b]
Dibasic Calcium Phosphate (b) (4)	USP	(b) (4)		(b) (4)
Sodium Starch Glycolate	NF			
Magnesium Stearate	NF			
Capsule Shell[e]	Manufacturer (DMF (b) (4)	Shell		
Total (Theoretical)	-	-	100.00	214.0[f]

a = (b) (4) w/w difference when compared with the approved PEXEVA tablets formula.
b = Equivalent to 7.5 mg of paroxetine base.
c = (b) (4) w/w difference when compared with the approved PEXEVA tablets formula.
d = No difference when compared with the approved PEXEVA tablets formula.
E = (b) (4)
f = Weight of capsule fill.

2.1.3 What are the proposed mechanism of action and therapeutic indication?

Indication:
Treatment of moderate to severe VMS associated with menopause.

Mechanism of Action:
Paroxetine is a selective serotonin reuptake inhibitor (SSRI). The mechanism of action of paroxetine mesylate with respect to treatment of VMS is unknown.

2.1.4 What are the proposed dose and dosing regimen?

The proposed dose is 7.5 mg once daily, at bedtime, with or without food.

2.1.5 What are the clinical and clinical pharmacology data submitted to support the approval of paroxetine mesylate 7.5 mg?

In support of this NDA, the Sponsor conducted a Phase I single- and multiple-dose PK study, a Phase II placebo-controlled proof-of-concept study, and two Phase III randomized, double-blind, placebo-controlled safety and efficacy studies. An overview of the clinical studies is presented in **Table 3**.

Table 3 Clinical studies for paroxetine mesylate 7.5 mg

Phase/ Study ID	Enrollment	Study Design	Study Duration
Phase I Study N30-005	N=24 healthy, postmenopausal women, ages 45-72	Uncontrolled single and 14-day repeat dose pharmacokinetic study Paroxetine mesylate 7.5 mg capsule	3 week screening, 1 day treatment (followed by 5 non-treatment days), 14 days treatment
Phase II Study N30-002	N=102 postmenopausal women, ages 40-67	8-week double blind, placebo controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	1 week placebo run-in period 8 week treatment period
Phase III Study N30-003	N=614 postmenopausal women, ages 40-79	12 week double blind, placebo-controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	7 day screening, 12-day placebo run-in period, 12 week treatment period
Phase III Study N30-004	N=570 postmenopausal women, ages 40-74	24-week double-blind, placebo-controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	7 day screening, 12-day placebo run-in period, 24 week treatment period

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of clinical studies used to support safety and efficacy?

The safety and efficacy of paroxetine 7.5 mg was supported primarily by two Phase III studies conducted in the U.S. (Study N30-003 and N30-004). Both studies were designed as randomized, double-blinded, placebo controlled, multi-center trials in postmenopausal women who had a mean total frequency of ≥ 56 moderate to severe VMS per week (≥ 7-8 per day on average) for 30 days prior to receiving study drug. Co-primary endpoints were reductions from baseline in hot flash frequency and hot flash severity at Week 4 and Week 12. Study N30-003 was a 12-week clinical trial, with a total of 614 postmenopausal women randomized 1:1 to receive paroxetine mesylate or placebo. This study also evaluated the clinical meaningfulness of the change from baseline in VMS frequency. Study N30-004 was a 24-week clinical study, with a total of 570 postmenopausal women randomized 1:1 to receive paroxetine mesylate or placebo, and also evaluated the persistence of benefit over 24 weeks of treatment.

The median age of the study subjects in two Phase III studies was 54 years old, ranged between 40 and 79 years old for study N30-003 and 40-74 years old for study N30-004. The majority of subjects (pool data of two Phase III studies) were White/Caucasian (approximately 70%) and not Hispanic/Latino (approximately 92%), and Black/African subjects were well represented (approximately 27%). The median BMI values were 29.47 kg/m^2 (16.79 ~ 60.67 kg/m^2) for study N30-003 and 27.49 kg/m^2 (18.26 ~ 40.6 kg/m^2) for Study N30-004. Approximately 70% of subjects in both studies were overweight (BMI, 25.0 ~ 30.0 kg/m^2) or obese (BMI, ≥ 30.0 kg/m^2).

2.2.2 What is the rationale for the proposed dose and dosing regimen?

The proposed dose is 7.5 mg once daily, at bedtime, with or without food.

Dose of 7.5 mg:

The Sponsor did not explore the dose-response relationship in the current submission. The only dose studied was the 7.5 mg. At the End-of-Phase 2 meeting (Meeting Minutes, DARRTS on 10/20/2010), the Sponsor noted that the selection of 7.5 mg dose was based on published literature where efficacy was seen with 10-25 mg of paroxetine. No apparent dose-response relationship was observed in the published literature. Therefore, the Sponsor selected 7.5 mg for their Phase III studies, a dose lower than that approved for psychiatric indications (10-60 mg), in order to have a dose that would likely show efficacy while also being safe and well-tolerated.

Dosing at bedtime:

Per Paxil® and Pexeva® labels, paroxetine should be taken in the morning. Interestingly, paroxetine 7.5

mg is proposed to be taken at bedtime. No scientific justification was provided in the current submission regarding the dosing time. Nonetheless, as the efficacy and safety of paroxetine 7.5 mg were assessed in Phase III studies at the same dosing regimen, the recommendation of dosing at bedtime is acceptable.

Dosing without regard to meal:
It should be noted that food effect study was not conducted for paroxetine 7.5 mg. Based on the information from Paxil® label, food does not affect paroxetine absorption. Considering that paroxetine is a Biopharmaceutics Classification System (BCS) class I drug and an immediate release (IR) formulation, it is expected that the bioavailability of paroxetine 7.5 mg will not be affected by food. In addition, efficacy and safety of paroxetine 7.5 mg were assessed in Phase III studies without restriction in food intake. Therefore, the recommended dosing regimen of taking with or without food is acceptable.

2.2.3 What are the single dose and multiple dose PK parameters for paroxetine 7.5 mg?

Study N30-005 characterized the PK profile of paroxetine after single and repeated oral doses of paroxetine 7.5 mg in the target population of postmenopausal women.

Study Design:
This was an open label, single- and repeated-dose study with paroxetine 7.5 mg in 24 healthy non-smoking postmenopausal women. On the evening of Day 0, the subjects checked in and had the baseline assessments for ECG, physical exam, etc. On Day 1, following overnight fasting and collection of baseline PK blood sample (within 30 minutes) and baseline vital signs, a single 7.5 mg paroxetine mesylate capsule was administered with 240 mL of water. Serial blood samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96 and 120 hours postdose. Starting on Day 6 (Day 6 through Day 19), the subjects took one paroxetine mesylate capsule daily for 14 days. Serial blood samples were collected at pre-dose on Day 18 and Day 19 and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours postdose on Day 19.

Study Results:
Following a single oral dose of paroxetine mesylate on Day 1, mean plasma concentrations of paroxetine reached a peak concentration at a median of 6 hours after dosing and started to decline exponentially with a mean half-life of 17.3 hours to less than 8% of the mean peak plasma concentration by 120 hours after dosing (**Figure 2**). Following multiple oral doses of paroxetine mesylate for 14 days, mean plasma concentrations of paroxetine reached a peak concentration at a median of 6 hours and started to decline within the dosing interval (τ =24 hours). The PK parameters of paroxetine are summarized in **Table 4.**
Cτ values after multiple doses on Day 18, Day 19 and Day 20 were similar suggesting the achievement of steady state by Day 18. Mean AUC_{0-24} of paroxetine after multiple doses at steady-state was 3.01 times greater than the mean AUC_{0-inf} observed after a single dose, suggesting time-dependent PK of paroxetine. The accumulation index calculated as the ratio of AUC_{0-24} at steady state to AUC_{0-24} after a single dose was 9.71. It should be noted that the PK parameters of paroxetine are highly variable. The large variability was also observed at other dose levels from Paxil® and Pexeva®. Factors that contribute to the variability of paroxetine PK parameters may include body weight, CYP2D6 polymorphism and gender (Feng, Pollock et al. 2006).

Figure 2 Mean (+SD) Paroxetine Concentration-Time Profiles after singe (Day 1) and repeated (Day 19) oral doses of paroxetine mesylate 7.5 mg (Linear Scale)

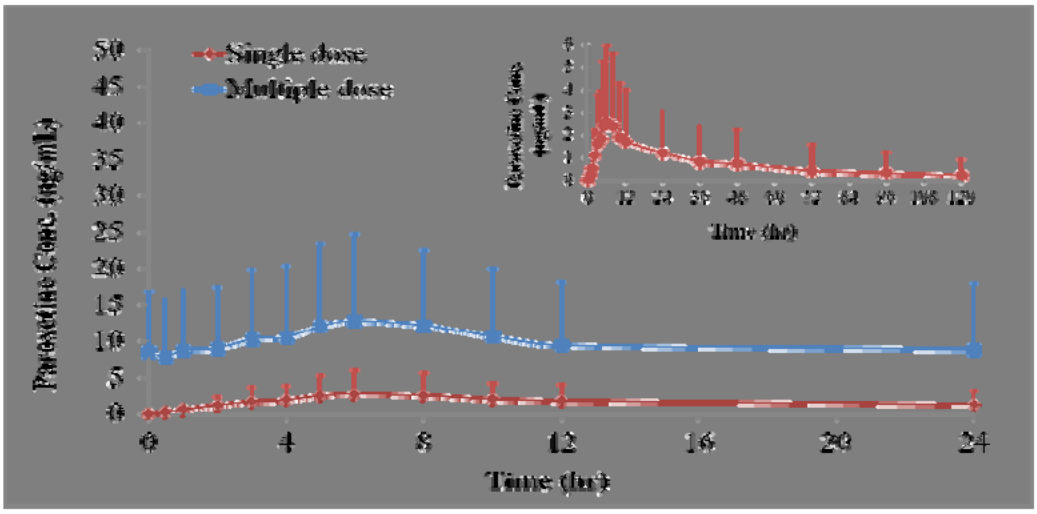


Table 4 Mean (CV%) Paroxetine PK Parameters after singe and repeated oral doses of paroxetine 7.5 mg (N=24)

PK parameters	Day 1	Day 19
$AUC_{0\text{-last}}$ (hr* ng/mL)	86.95 (191.13)	237.34 (93.81)
$AUC_{0\text{-inf}}$ (hr* ng/mL)	78.80 (240.97)[a]	-
$AUC_{0\text{-}24}$ (hr* ng/mL)	38.90 (133.25)	237.28 (93.83)
C_{max} (ng/mL)	2.77 (122.20)	13.10 (91.03)
T_{max} (hr) [b]	6.00 (1.00, 8.00)	6.00 (3.00, 8.00)
K_{el} (hr^{-1})	0.05 (28.43)[a]	-
$T_{½}$ (hr)	17.30 (66.17)[a]	-
C_{min} (ng/mL)	-	7.67 (98.68)
C_{avg} (ng/mL)	-	9.89 (93.83)
Fluctuation Index [c] (%)	-	75.76 (35.57, 153.20)
Accumulation index [c]		9.71 (0.12, 23.48)

a N=23; for subject 001-019, k_{el} and its associated parameters are not reported since the percent extrapolation of $AUC_{0\text{-inf}}$ was greater than 25%.
b Median (range) is presented for Tmax.
c Mean (minimum, maximum) is presented for Fluctuation Index and Accumulation Index.
On Day 19, the 24 hour post dose sample for subject 013 was re-assayed. This 24 hour sample was excluded from PK parameter estimation in this table.

2.2.4 What are the PK characteristics of drug absorption?

Based on the information from Paxil® label, paroxetine is completely absorbed from the GI tract after oral dosing and undergoes extensive first pass metabolism. The absolute bioavailability was reported to be about 50% after a single dose (Hiemke and Hartter 2000). Paroxetine is equally bioavailable as hydrochloride salt and as mesylate salt. The absorption of paroxetine is not affected by the presence of food. In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. C_{min} values after 40 mg paroxetine were only about 2 to 3 times greater than that from 20 mg daily dose.

2.2.5 What are the characteristics of drug distribution?

Based on the information from Paxil® label, paroxetine distributes throughout the body including the CNS, with only 1% remaining in the plasma. Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical dose of VMS indication, paroxetine concentrations would be much lower than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

2.2.6 What are the characteristics of drug metabolism?

Based on the information from Paxil® label, paroxetine is extensively metabolized after oral administration. The metabolism of paroxetine is accomplished in part by cytochrome CYP2D6. It has been speculated that paroxetine is metabolized via 2 parallel pathways: a high-affinity, low capacity process dependent on CYP2D6 and a low-affinity, high-capacity process medicated by other enzymes with CYP3A4 being a possibility (Sindrup, Brosen et al. 1992) (Jornil, Jensen et al. 2010). Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. Metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake and are considered to be inactive.

2.2.7 What are the characteristics of drug excretion?

The mean elimination half-life of paroxetine is about 17 hours after a single dose of 7.5 mg paroxetine. Based on the information from Paxil® label, approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day postdosing period.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, BMI, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal or Hepatic Impairment

Based on the information from Paxil® label, paroxetine exposure ($AUC_{0\text{-}inf}$) in patients with creatinine clearance (CrCl) below 30 mL/min were approximately 4 times greater than those in healthy volunteers with normal renal function. Patients with CrCl of 30 to 60 mL/min and patients with hepatic impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}). It should be noted that paroxetine is extensively metabolized, thus renal impairment is not expected to affect paroxetine exposure. However, this is not case as shown from the study results. The mechanism behind is not known.

No dose adjustment is necessary considering that the current dose (7.5 mg/day) is lower than 10 mg/day, the recommended initial dose for patients with severe renal or hepatic impairment for psychiatric indications.

BMI

The Sponsor conducted a subgroup analysis to assess the effect of BMI on paroxetine efficacy for VMS treatment. The analysis data suggested that BMI might affect the treatment outcome of paroxetine. In particular, the mean weekly reduction in the frequency of moderate to severe hot flashes from Baseline to Week 12 (Study N30-003) or to Week 24 (Study N30-004) was significantly greater for the paroxetine group than for the placebo group in the BMI <32 kg/m^2 subgroup but not in the BMI ≥ 32 kg/m^2 subgroup. However, per Statistic reviewer, Dr. Jia Guo, the sub-group analysis may not have enough statistic power and should be treated as exploratory analysis.

Geriatric

Clinical studies of paroxetine 7.5 mg did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients. In particular, the elderly subjects ($\geq$65 years) only represented about 6% of study subjects in the pivotal Phase III studies of paroxetine 7.5 mg.

Based on the information from Paxil® label, the minimum plasma (C_{min}) concentrations in elderly subjects were about 70% to 80% higher than the respective C_{min} in nonelderly subjects. Nonetheless, dose adjustment is not considered necessary for elderly patients considering the low dose (7.5 mg) relative to approved paroxetine doses (10 - 60 mg) for the psychiatric indications.

Pediatric
The Sponsor has requested a waiver for all pediatric age groups, neonates through adolescents, as paroxetine 7.5 mg is not indicated in this population.

2.4 EXTRINSIC FACTORS

2.4.1 What DDI information is available for paroxetine from Paxil® and Pexeva® labels?

The DDI information from Paxil® and Pexeva® labels is summarized below.

PK-based DDI: Effect of other drugs on paroxetine:
Concomitant use of paroxetine with other drugs that alter CYP enzymes activities may affect the plasma concentrations of paroxetine (**Table 5**)

Table 5 Effect of other drugs on paroxetine

Concomitant Drug	Effect on drug conc.	Clinical Comments
Cimetidine	↑ 50%	No dose adjustment
Phenobarbital	↓ 25%	No dose adjustment
Phenytoin	↓ 50%	No dose adjustment
Diazepam	⇔	
Fosamprenavir/Ritonavir	↓ significantly	
Drugs highly bound to plasma protein	↑	Caution

PK-based DDI: Effect of paroxetine on other drugs
Paroxetine causes irreversible auto-inhibition of CYP2D6 by formation of a metabolite inhibitory complex with the heme iron. Concomitant use of paroxetine with other drugs metabolized by
CYP2D6 may lead to a substantially increase systemic exposure and may require lower doses than usually prescribed for the other drug (**Table 6**).

Table 6 Effect of paroxetine on other drugs

Concomitant Drug	Effect on drug conc.	Clinical Comments
Thioridazine	↑, QT prolongation	Contraindication
Pimozide	↑ 151%, QT prolongation	Contraindication
Tamoxifen	↓ Active metabolites	An alternative treatment with little or no CYP2D6 inhibition
Desipramine	↑ 500%	
Risperidone	↑ 140% active moiety	
Atomoxetine	↑ 600-800%	atomoxetine dose reduction
Tricyclic Antidepressants:	↑	Caution, monitoring for dose adjustment
Digoxin	↑ 15%	Caution
Procyclidine	↑ 35%	procyclidine dose reduction
Beta Blocker: propranolol	⇔	
Theophylline	↑ Case reports	Monitoring theophylline concentrations
Drugs highly bound to plasma protein	↑	Caution

Co-administration of paroxetine 7.5 mg with other drugs that are metabolized by this isozyme, including

certain drugs effective in the treatment of major depressive disorder (MDD) (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

Table 7 Other interactions included in the label:

Concomitant Drug	Clinical Observation	Clinical Comments
Serotonergic Drugs: Triptans, tricyclic antidepressants, linezolid, lithium, tramadol, tryptophan supplements, or St. John's Wort	Adverse reactions	No concomitant use of paroxetine with other SSRIs, SNRIs or tryptophan
Central Nervous System (CNS)-Active Agents	Risk of concomitant use has not been systemically evaluated	Caution
Ethanol		Avoid alcohol while taking paroxetine
Drugs that Interfere with Hemostasis NSAIDs, Aspirin, and Warfarin	Increased risk of bleeding	Caution

2.4.1 How is the DDI information from Paxil label extrapolated to paroxetine mesylate 7.5 mg for the VMS indication?

There were no DDI studies conducted for paroxetine mesylate 7.5 mg capsule. The Sponsor is proposing to use the DDI information from Paxil® and Pexeva® labels. It should be noted that the majority of the DDI studies examining the effect of paroxetine on the exposure of CYP2D6 substrates used a daily paroxetine dose of 20 mg/day or higher. During the pre-NDA meeting held on May 29, 2012, the Sponsor was requested to address whether the information from these DDI studies can be extrapolated to paroxetine 7.5 mg. The Sponsor justified in the current submission that paroxetine 7.5 mg will carry a similar DDI potential based on the following reasons:

- Some clinical DDI studies have demonstrated that paroxetine at doses as low as 10 mg/day causes prolonged inhibition of CYP2D6 substrates, particularly after dosing paroxetine to steady state concentrations.
- The saturation of CYP2D6 metabolic capacity accounts for the nonlinear paroxetine PK observed with increasing doses or multiple dosing. Nonlinear PK due to auto-inhibition of CYP2D6 was confirmed in the PK study following once a day multiple administrations of the 7.5 mg oral dose (Study N30-005).

This reviewer agrees that the DDI information in the Paxil® and Pexeva® labels can be extrapolated to the current product. Multiple administration of paroxetine 7.5 mg may still result in a significant inhibition of CYP2D6 activity.

Paroxetine and Tamoxifen:

Currently, hormone therapy is the only approved treatment for VMS associated with menopause. If approved, paroxetine will be the 1st non-hormonal product for the VMS treatment and is likely to be prescribed to women who have contraindications to hormonal therapy. Some of these women may be breast cancer patients who are taking tamoxifen therapy.

- Mechanism of drug interaction

Tamoxifen is metabolized by a number of CYP enzymes, such as CYP2D6, CYP3A4, CYP2C9, CYP2C19, and CYP2B6 to active metabolites, N-desmethyl tamoxifen and 4-hydroxytamoxifen. N-desmethyl tamoxifen is further metabolized by CYP2D6 to endoxifen, an entity responsible for significant pharmacologic effect of tamoxifen. As a potent CYP2D6 inhibitor, paroxetine can reduce

endoxifen concentrations and thus may compromise tamoxifen efficacy.

- Study reports on paroxetine and tamoxifin drug interaction
    - Effect of paroxetine on endoxifen exposure:
      Sterns and coworkers showed that endoxifen exposure was decreased by 64% following the paroxetine dosing regimen of 10 mg/day for 4 weeks due to the interaction through CYP2D6 (Stearns, Johnson et al. 2003).
    - Effect of paroxetine on tamoxifen therapeutic outcome
      As of today, over 20 published studies have reported on the impact of CYP2D6 inhibition /CYP2D6 polymorphism on tamoxifen treatment outcome, as measured by the risk of breast cancer replase/mortality. However, the study results are controversial (Hertz, McLeod et al. 2012).

- Labeling Recommendation

Considering the benefit and risk of paroxetine use in patients taking tamoxifen, Office of Clinical Pharmacology recommends "consider avoiding the concomitant use of paroxetine in women taking tamoxifen". The detailed labeling recommendation is listed as following:
"It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 [see Drug Interactions (7.7)]. However, other studies have failed to demonstrate such a risk. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers may consider avoiding the concomitant use of paroxetine for the treatment of VMS."

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Is the clinical trial formulation same as the TBM formulation?

Yes. This is an IR 7.5 mg capsule. It contains 9.69 mg of paroxetine mesylate (equivalent to 7.5 mg of paroxetine base) filled in a Size 3 hard gelatin capsule. The composition of and function of each components of the capsule are shown in **Table 2.**

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess the plasma concentration of paroxetine?

Blood samples were collected for the determination of paroxetine in plasma using a validated LC/MS/MS. Precision and accuracy criteria were met for quality control (QC) samples and calibration standard samples. Incurred sample reanalysis (ISR) met the acceptance criteria (Study report: 110513AKJC_NMF). Summary of bioanalytical methods is presented in **Table 8**.

Table 8 Summary of Bioanalytical Methods for Paroxetine

Internal Standard	Paroxetine-d_4
Range of Standard Curve	0.025 - 25 ng/mL
QC sample accuracy (% Dev)	2.9 – 3.7 %
QC sample precision (% CV)	≤ 5.9 %
Calibration Standards accuracy (% Dev)	-2.6 to 2.4%
Calibration Standards precision (% CV)	≤ 5.0 %
Stability at -20 ºC and -70 ºC	101 days

3 LABELING RECOMMENDATIONS

Detailed labeling recommendations will be incorporated into DBRUP's proposed label.

The Clinical Pharmacology relevant edits to the proposed label include the following:

- Currently, all the DDI information is presented under Section 7 (DDI section). Based on 21CFR 201.57 (C)(8) or the 2012 *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* guidance (Pages 59-60) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf),
    - The detailed information of the DDI study should be moved to Section 12 (clinical pharmacology section).
    - Considering the extensive drug interaction studies, we recommend the use of table(s) to convey the PK drug interactions (the pharmacodynamic interactions can be included in the text in subsections). In the table, the "Clinical Recommendations" column includes recommendations for dosage adjustments, monitoring, and contraindications (Tables below).
    - Include a cross-reference to the Pharmacokinetic subsection in the Clinical Pharmacology section for the details of the PK studies.

Table 1: Effects of Concomitant Drugs on Paroxetine

Concomitant Drug Name	Effect of Concomitant Drug on Paroxetine	Clinical Recommendations

Table 2: Effects of Paroxetine on Other Drugs

Concomitant Drug Name	Effect of Paroxetine on Other Drugs	Clinical Recommendations

- The effect of food on paroxetine absorption will be added to section 12.3 under Absorption subsection.
- The description of protein binding will be moved to Distribution subsection.

4 APPENDIX
4.1 INDIVIDUAL STUDY REVIEW

4.4.1 Single and repeated-dose PK study: Study N30-005

Evaluation of Pharmacokinetics of Paroxetine following Single and Repeated Oral administration of 7.5 mg Paroxetine Mesylate Capsules in Healthy Postmenopausal Women

Protocol No:	N30-005
Phase:	1
Principal Investigator:	Dr. Mohamed Al-Ibrahim
Clinical Study Center:	SNBL Clinical Pharmacology Center, 800 West Baltimore Street Baltimore, MD 21201
Clinical Study Dates:	July ~ August, 2011
Analytical Study Facility:	(b) (4)

OBJECTIVES

- To study the PK of paroxetine after single and repeated doses
- To assess the safety and tolerability of paroxetine after single and repeated doses

STUDY DESIGN

This was an open label, single- and repeated-dose study with 7.5 mg paroxetine mesylate in 24 healthy non-smoking postmenopausal women. On the evening of Day 0, the subjects checked in and had the baseline assessments for ECG, physical exam, C-SSRS, drug and alcohol screen and collection of AEs and concomitant medications. On Day 1, following overnight fasting and collection of baseline PK blood sample (within 30 minutes) and baseline vital signs, a single 7.5 mg paroxetine mesylate capsule was administered with 240 mL of water. Serial blood samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96 and 120 hours postdose. Starting on Day 6 (Day 6 through Day 19), the subjects took one paroxetine mesylate capsule daily for 14 days. Serial blood samples were collected at pre-dose on Day 18 and Day 19 and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours postdose on Day 19.

Disposition of Study Subjects

Twenty four healthy non-smoking postmenopausal women enrolled and completed the study. The age of study subjects ranged 45-72 years old with average body weight of 75.4 kg (range: 54-106 kg). Of the 24 subjects, there were 12 white, 11 Africa America and 1 American Indian or Alaskan Native. Most subjects (22) were not Hispanic or Latino.

Inclusion Criteria

- Subjects who are willing and able to be compliant with the protocol and provide voluntary written informed consent voluntary written informed consent.
- Subjects who are healthy postmenopausal, non-smoking women of any race and ≥ 40 years of age at screening (inclusive). Note: for postmenopausal status subjects must meet one of the following criteria:
  - Spontaneous amenorrhea for at least 12 consecutive months
  - Amenorrhea for at least 6 months and meet the biochemical criterion for menopause (follicle-stimulating hormone, FSH ≥ 40 mIU/mL)
  - Bilateral salpingo-oophorectomy ≥ 6 weeks with or without hysterectomy (documentation of bilateral oophorectomy surgery must be available for review).

- Subjects who are judged by the Investigator and the Sponsor to be healthy on the basis of screening

medical history, physical examination, electrocardiogram, and clinical laboratory test results.
- Subjects who are willing to consume the entire contents of meals served while in house AND have no relevant food allergies.

Exclusion Criteria
- Subjects who have a recent history or presence of glaucoma, migraines, cardiovascular, hepatobiliary, renal, gastrointestinal, neurologic, psychiatric, dermatologic, pulmonary, cerebrovascular, endocrine, hematologic, thromboembolic, immunologic disease or any other disorder which requires physician care.
- Subjects who have existing medical conditions which might interfere with absorption, distribution, metabolism, or excretion of study medication.
- History of self-injurious behavior
- History of clinical diagnosis of depression; or treatment for depression
- History of clinical diagnosis of border-line personality disorder
- Presence of any of the certain psychiatric disorders within different timeframe (detail in the study protocol)
- Subjects with a history of seizures.
- Sitting blood pressure (BP) < 90/50 or > 150/90 mmHg.
- Sitting heart rate (HR) < 45 or > 90 beats/min.
- Clinical laboratory test results outside of the normal range for the laboratory conducting the test (unless judged by the Sponsor and the Investigator not clinically significant).
- Positive urine pregnancy test at Screening or Day 0.
- Subjects who have a history of sensitivity to paroxetine, related derivatives, or any of the inactive ingredients in paroxetine mesylate capsules.
- Subjects who have a history of significant allergies (including food, asthma, or drug allergies).
- Subjects who have a present or past history of narcotic addiction, drug abuse, or alcoholism.
- Subjects who have smoked or used tobacco during the last 6 months.
- Subjects who have donated one or more pints of blood within 30 days prior to treatment.
- Subjects who have symptoms of any significant acute illnesses at the screening visit.
- Subjects who used any investigational drug within 30 days prior to treatment
- Subjects who took any substances known to be CYP 2D6 inhibitors within 14 days of study start and throughout the entire study.
- Subjects who used any prescription medications within 14 days of the screening visit.
- Subjects who used St John's Wort within 14 days of the screening visit.
- Subjects who used any over the counter preparations including herbal or nutritional supplements and multivitamins within 10 days prior to receiving the first study treatment.
- Subjects who have consumed foods or beverages containing caffeine/xanthine or alcohol within 72 hours prior to receiving the first study treatment.
- Subjects who have a positive screen for hepatitis B surface antigen (HBsAg) or hepatitis C antibody.
- Subjects who have a positive screen for the Human Immunodeficiency Virus (HIV) antibody.
- Subjects who have a positive urine drug screen.
- Subjects who have any clinically significant illness within 90 days prior to receiving the first dose of study medication.

Formulations
For this trial, each paroxetine mesylate capsule was a white hard gelatin #3 capsule containing paroxetine mesylate equivalent to paroxetine as follows: 7.5 mg Paroxetine Mesylate (as paroxetine), Dibasic Calcium Phosphate (USP), Sodium Starch Glycolate (NF) and Magnesium Stearate (NF).

Concomitant Food, Drinks and Therapy
Subjects were prohibited from taking or using prescription medications, over-the-counter products, including multivitamins, herbal (e.g., St. John's Wort) or nutritional supplements, investigational

products, tobacco, or drugs of abuse. Subjects were also prohibited from donating blood or engaging in strenuous exercise.

Protocol Deviation
Two subjects received concomitant medication during the 10-hour periods proceeding and following study drug administration. Subject 10 received gemfibrozil three minutes before the end of the 10-hour period during the first period. Subject 20 received Humalog 16 minutes after the beginning and 11 minutes before the end of the 10-hour period during the first period, and received Humalog, Altace, aspirin and Coreg 11, 6, 6, and 6 minutes, respectively, before the end of the 10-hour period during the second period.

PHARMACOKINETIC EVALUATION
Blood Sampling
Blood samples to be used for drug concentration measurement were to be collected at the following time points:

- Day 1 - Day 6: pre-dose (within 30 min) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours following dose administration at t=0 on Day 1 (17 samples)
- Day 18: pre-dose, immediately prior to dosing (one sample)
- Day 19 - Day 20: pre-dose (immediately prior dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours following dose administration on Day 19 (12 samples)

Bioanalytical method
Blood samples were collected for the determination of paroxetine in plasma using a validated LC/MS/MS. Precision and accuracy criteria were met for QC samples and calibration standard samples. Incurred sample reanalysis met the acceptance criteria (Study report: 110513AKJC_NMF). Summary of bioanalytical methods is presented in **Table 1**. Validation of the methodology was completed prior to assay of test samples.

Table 1 Summary of Bioanalytical Methods for Paroxetine

Internal Standard	Paroxetine-d_4
Range of Standard Curve	0.025 - 25 ng/mL
QC sample accuracy (% Dev)	2.9 – 3.7 %
QC sample precision (% CV)	≤ 5.9 %
Calibration Standards accuracy (% Dev)	-2.6 to 2.4%
Calibration Standards precision (% CV)	≤ 5.0 %
Stability at -20 ºC and -70 ºC	101 days

SAFETY ASSESSMENTS
Most subjects (23/24) experienced at least one treatment emergent adverse events (TEAE) (73 events in total) and most of the TEAEs were mild in severity (22/24). By severity, mild TEAEs occurred with the highest incidence (91.7%) and by relationship, unrelated TEAEs occurred with the highest incidence (75.0%). There were no deaths or other serious adverse events, no discontinuations due to AEs and no severe TEAEs. Of the 33 probably and possibly related TEAEs that occurred in the trial slightly more than half (17) were reported by two subjects (001-020 and 001-024). These two subjects also reported more discontinuation emergent signs and symptoms scale (DESS) new symptoms than the other 22 subjects (five each versus three or less). Due to the small sample size of this trial, it is not possible to determine whether these results are meaningful.

DATA ANALYSIS

The plasma concentration over time profiles were analyzed by non-compartmental methods using Phoenix WinNonlin version 6.1 and AUCs were calculated using the linear trapezoidal method. For the estimation of apparent elimination rate constant k_{el}, at least 3 quantifiable time points (not including C_{max}) and goodness of fit (r^2) greater than 0.9 were required to retain k_{el} and its associated parameters (AUC0-inf and t1/2). Percent extrapolation cut-off of 25% was used for accepting AUC0-inf and its associated parameters (k_{el} and $t_{1/2}$).

PHARMACOKINETIC RESULTS

Following a single oral dose of paroxetine mesylate on Day 1, mean plasma concentrations of paroxetine reached a peak concentration at a median of 6 hours after dosing and started to decline exponentially with a mean half-life of 17.3 hours to less than 8% of the mean peak plasma concentration by 120 hours after dosing (**Figure 1**). Following multiple oral doses of paroxetine mesylate on Day 19, mean plasma concentrations of paroxetine reached a peak concentration at a median of 6 hours and started to decline within the dosing interval (τ =24 hours). The PK parameters of paroxetine are summarized in **Table 1.** Cτ values after multiple doses on Day 18, Day 19 and Day 20 were similar suggesting the achievement of steady state by Day 18. Mean AUC_{0-24} of paroxetine after multiple doses at steady-state was 3.01 times higher than the mean AUC_{0-inf} observed after a single dose. The accumulation index calculated as the ratio of AUC_{0-24} at steady state to AUC_{0-24} after a single dose was 9.71.

Figure 1 Mean (+SD) Paroxetine Concentration-Time Profiles following and single and repeated dose of paroxetine mesylate 7.5 mg (Linear Scale)

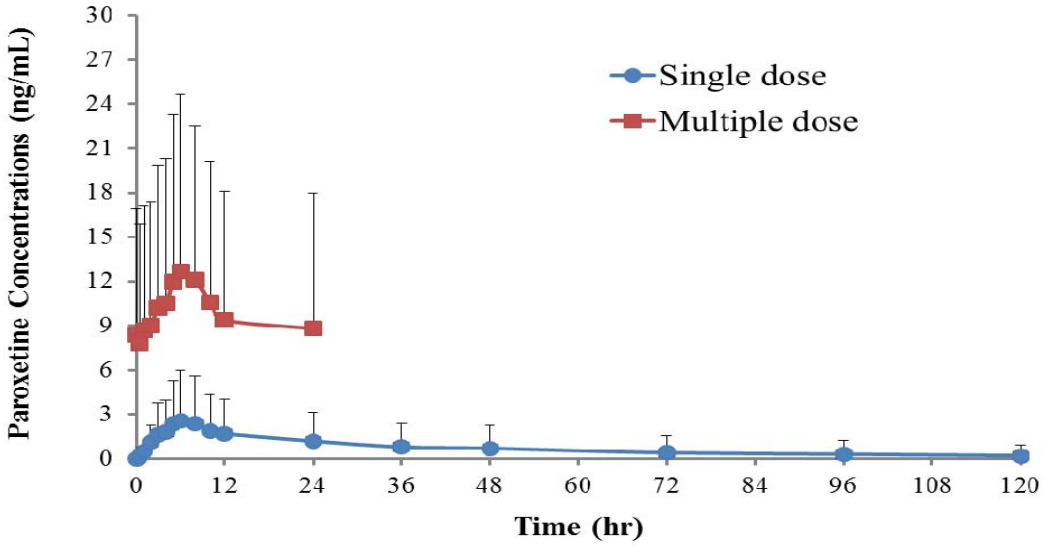


Table 1 Mean (CV%) Paroxetine PK Parameters by Day

PK Parameter (unit)	Day 1 (N = 24)	Day 19 (N = 24)
$AUC_{0\text{-last}}$ (hr*ng/mL)	86.95 (191.13)	237.34 (93.81)
$AUC_{0\text{-inf}}$ (hr*ng/mL)	78.80 (240.97) [a]	.
$AUC_{0\text{-}24}$ (hr*ng/mL)	38.90 (133.25)	237.28 (93.83)
C_{max} (ng/mL)	2.77 (122.20)	13.10 (91.03)
T_{max} (hr)[b]	6.00 (1.00, 8.00)	6.00 (3.00, 8.00)
K_{el} (hr^{-1})	0.05 (28.43) [a]	.
$t_{1/2}$ (hr)	17.30 (66.17) [a]	.
C_{min} (ng/mL)		7.67 (98.68)
$C_{avg,ss}$ (ng/mL)		9.89 (93.83)
Fluctuation Index[c] (%)		75.76 (35.57, 153.20)
Accumulation Index[c]		9.71 (0.12, 23.48)
$C_{\tau 18}$ (ng/mL)		8.53 (107.52)
$C_{\tau 19}$ (ng/mL)		8.35 (101.63)
$C_{\tau 20}$ (ng/mL)		8.79 (104.50)

[a] N=23; for subject 001-019, k_{el} and its associated parameters are not reported since the percent extrapolation of $AUC_{0\text{-inf}}$ was greater than 25%.
[b] Median (range) is presented for T_{max}.
[c] Mean (minimum, maximum) is presented for Fluctuation Index and Accumulation Index.
On Day 19, the 24 hour post dose sample for subject 013 was re-assayed. This 24 hour sample was excluded from PK parameter estimation in this table.

Reviewer's comment:

- *The overall study design and data analysis appear acceptable.*
- *Large PK variability of paroxetine was observed in the current study. Specifically, the variability associated with total and peak exposures of paroxetine (as assessed by coefficient of variation [CV] %) exceeded 90% following single and multiple oral doses of 7.5 mg paroxetine. This is consistent with the observation from other studies with paroxetine.*
- *In addition to genetic factors (CYP2D6 polymorphism), body weight might be another significant variability factor for paroxetine based on a population PK analysis in late-life depression.(Feng, Pollock et al. 2006; Gex-Fabry, Eap et al. 2008)*
- *There was no genotype/phenotype screen for subjects in the current study.*

REFERENCES

*Feng, Y., B. G. Pollock, et al. (2006). "Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling." Br J Clin Pharmacol **61**(5): 558-569.*

*Gex-Fabry, M., C. B. Eap, et al. (2008). "CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response." Ther Drug Monit **30**(4): 474-482.*

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*Sindrup, S. H., K. Brosen, et al. (1992). "Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine: nonlinearity and relation to the sparteine oxidation polymorphism." Clin Pharmacol Ther **51**(3): 288-295.*

*Stearns, V., M. D. Johnson, et al. (2003). "Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine." J Natl Cancer Inst **95**(23): 1758-1764.*

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/s/

LI LI
05/17/2013

MYONG JIN KIM
05/17/2013
I concur.

BIOPHARMACEUTICS NDA REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-516	**Reviewer:** Deepika Arora Lakhani, PhD	
Submission Date:	28-AUG-2012 12-DEC-2012		
Division:	Division of Reproductive and Urologic Drug Products	**Secondary Signature:** Sandra Suarez, PhD	
Sponsor:	Noven Therapeutics	**Biopharmaceutics Supervisor (Acting):** Richard Lostritto, PhD	
Trade Name:	(b) (4)™ (Proposed)	**Date Assigned:**	Oct 15, 2012
Generic Name:	Paroxetine Mesylate	**Date of Review:**	Apr 24, 2013
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause	**Type of Submission:** New Drug Application 505b(2)	
Formulation/ strengths	Capsules, 7.5 mg		
Route of Administration	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

The NDA submission is a 505(b)(2) application for Paroxetine mesylate, a selective serotonin reuptake inhibitor, that was previously approved as 10, 20, 30, and 40 mg paroxetine (as mesylate) tablets (PEXEVA® [paroxetine {as mesylate}] tablets) under NDA 21-299. The Applicant for the current NDA and for the approved Pexeva® tablets is the same (Noven Therapeutics). (b) (4)

This review focuses on evaluating the acceptability of the proposed dissolution method and acceptance criteria and the use of dissolution to support two drug product manufacturing sites: Norwich Pharmaceuticals, Inc. (Norwich, NY) and (b) (4)

1. Dissolution Method and Acceptance Criterion:

The following method to assay the dissolution of paroxetine mesylate tablets was developed:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criterion
Paroxetine Mesylate	Tablet	II (paddle)	75	simulated gastric fluid (pH 1.20 ± 0.05)	900 mL	Q= (b) (4) at 20 minutes

The discriminating capacity of the dissolution method was evaluated by showing that the method is able to detect differences in formulation that are impaired by exposure to light. The proposed dissolution method discriminated for photo-unstable drug product and has been deemed acceptable. During a teleconference dated April 25, 2013 the Applicant was advised, based on the provided mean dissolution data from clinical and stability batches, to (b) (4) the dissolution acceptance criterion from Q= (b) (4) to Q= (b) (4) at 20 min. The Applicant mentioned the need of further verification of the appropriateness of this FDA's recommended acceptance criterion and committed to send a response to either 1) Agree with the FDA's recommended acceptance criterion or 2) Submit statistical data supporting a (b) (4) value. The

Applicant's response is still awaited and has not been received as of April 26, 2013.

2. Assessment of the Dissolution Data to Support the Two Drug Product Manufacturing Sites:
The Applicant has contracted two drug product manufacturers for its paroxetine mesylate capsules, 7.5 mg (paroxetine mesylate capsules) product. The two manufacturers are Norwich Pharmaceuticals, Inc. (Norwich, NY) and (b) (4) In order to compare drug product manufactured at each of the two manufacturing sites, three batches of drug product from each of the manufacturing sites were compared head-to-head using the proposed dissolution conditions. The dissolution profile comparison and calculation of f2 supports the sameness of drug product manufactured at the two sites.

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed NDA 204-516 and its amendment submitted on 12-DEC-2012 and 25-APR-2013. The following dissolution method for paroxetine mesylate capsules is deemed acceptable:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
Paroxetine Mesylate	Capsule	II (paddle) with wire sinkers	75	simulated gastric fluid (pH 1.20 ± 0.05)	900 mL

The following dissolution acceptance criterion has been recommended for paroxetine mesylate capsules:

Q= (b) (4) at 20 minutes

From the Biopharmaceutics perspective an APPROVAL recommendation for NDA 204-516 for (b) (4) (paroxetine mesylate) Capsules cannot be granted as of April 26, 2013 due to the following pending information/agreement:

- Agreement upon the recommended dissolution acceptance criterion

Note that these pending data will be submitted during this review cycle. It is expected that the Biopharmaceutics team and the Applicant will reach an agreement on the appropriate dissolution acceptance criterion and will recommend APPROVAL of this NDA during this review cycle.

Deepika Arora Lakhani, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, PhD
Secondary Signature
Office of New Drug Quality Assessment

cc. *on file; RLostritto, ADorantes*

(b) (4)™ Capsules

Noven Therapeutics, LLC

BIOPHARMACEUTICS ASSESSMENT

INTRODUCTION

The proposed drug product is an immediate-release, solid oral-dosage form of paroxetine mesylate as a capsule. The Applicant currently holds NDA 21-299 for another immediate-release solid oral dosage form of paroxetine mesylate (PEXEVA® Tablets), which is marketed in strengths of 10, 20, 30, and 40 mg. (b) (4) A comparison of the approved tablet formulation and the proposed capsule formulation is shown below:

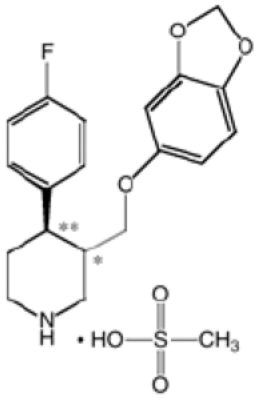
Table 1. Comparison of Composition between PEXEVA® Tablets, 10 mg and Proposed Paroxetine Capsules, 7.5 mg

	PEXEVA Tablets, 10 mg		Paroxetine Capsule, 7.5 mg	
Component	**mg/Tablet**	**% w/w**	**mg/Capsule**	**% w/w**
Paroxetine Mesylate	(b) (4)		9.69[a]	(b) (4)
Dibasic Calcium Phosphate (b) (4)			(b) (4)	
Sodium Starch Glycolate				
Magnesium Stearate				
Total Weight	178.27 mg	100.0%	214.0 mg	100.0%

[a] = Equivalent to 10 mg or 7.5 mg of paroxetine base.

Drug Substance

Paroxetine mesylate is very soluble over the pH covering the physiological range. The pH solubility profile of the drug substance is shown in Table 2.



paroxetine mesylate

Figure 1. Chemical Structure of Paroxetine Mesylate

Table 2. Solubility profile of Paroxetine mesylate

Medium	Solubility (mg/mL)
0.01 M HCl, pH=1.0	>1000
SGF (without pepsin), pH=1.2	>1000
0.016 M Acetate buffer, pH=4.0	>1000
Purified Water	>1000
0.047 M Phosphate, pH=7.5	>1000

Drug Product

The Drug Product contains 9.69 mg of paroxetine mesylate (equivalent to 7.5 mg of paroxetine base) in a size 3, opaque pink/pink body and cap, hard gelatin capsule. The quantitative composition of the capsule is provided in Table 3.

Table 3. Quantitative Composition of Drug Product

Component	Reference to Quality Standards	Function	% w/w	mg/capsule
Paroxetine Mesylate	In-house (NDA 21-299)	Drug substance	(b) (4)	9.69[a,b]
Dibasic Calcium Phosphate (b) (4)	USP	(b) (4)		(b) (4)
Sodium Starch Glycolate	NF			
Magnesium Stearate	NF			
Capsule Shell[e]	Manufacturer (b) (4)	Shell		
Total (Theoretical)			100.00	214.0[f]

[a] = (b) (4) w/w difference when compared with the approved PEXEVA tablets formula.
[b] = Equivalent to 7.5 mg of paroxetine base.
[c] = (b) (4) w/w difference when compared with the approved PEXEVA tablets formula.
[d] = No difference when compared with the approved PEXEVA tablets formula.
[e] = (b) (4)
.
= Weight of capsule fill.

Formulation Development

Other than the tablet-to-capsule conversion, there are minimal changes to the formulation from the approved Pexeva® tablets (see Table 1). There were no changes made to the quantitative and qualitative compositions of paroxetine mesylate capsules, 7.5 mg during the development phase. A comparison of all Clinical, Registration and Commercial Batch Formulae for Paroxetine (as Mesylate) Capsules, 7.5 mg is shown below in Table 4.

Table 4. Clinical, Registration and Commercial Batch Formulae for Paroxetine (as Mesylate) Capsules, 7.5 mg

Bulk Capsule Batch No.	**432207**	**439462**	**444141 444253**	**444252**	**NA**
Batch Use	Phase 2 Clinical	Phase 3 Clinical	Registration (Pilot Scale)	Registration (Commercial Scale)	Commercial
Batch Size (Capsules)	(b) (4)				
Components	**mg/capsule**				
Paroxetine Mesylate	9.69 mg [a]	9.69 mg [a]	9.69 mg [a]	9.69 mg [a]	9.69 mg [a]
Dibasic Calcium Phosphate (b) (4), USP	(b) (4)				
Sodium Starch Glycolate, NF					
Magnesium Stearate, NF					
Total	214.00	214.00	214.00	214.00	214.00
(b) (4)	1	1			
			1	1	
					1

= Equivalent to 7.5 mg paroxetine base.

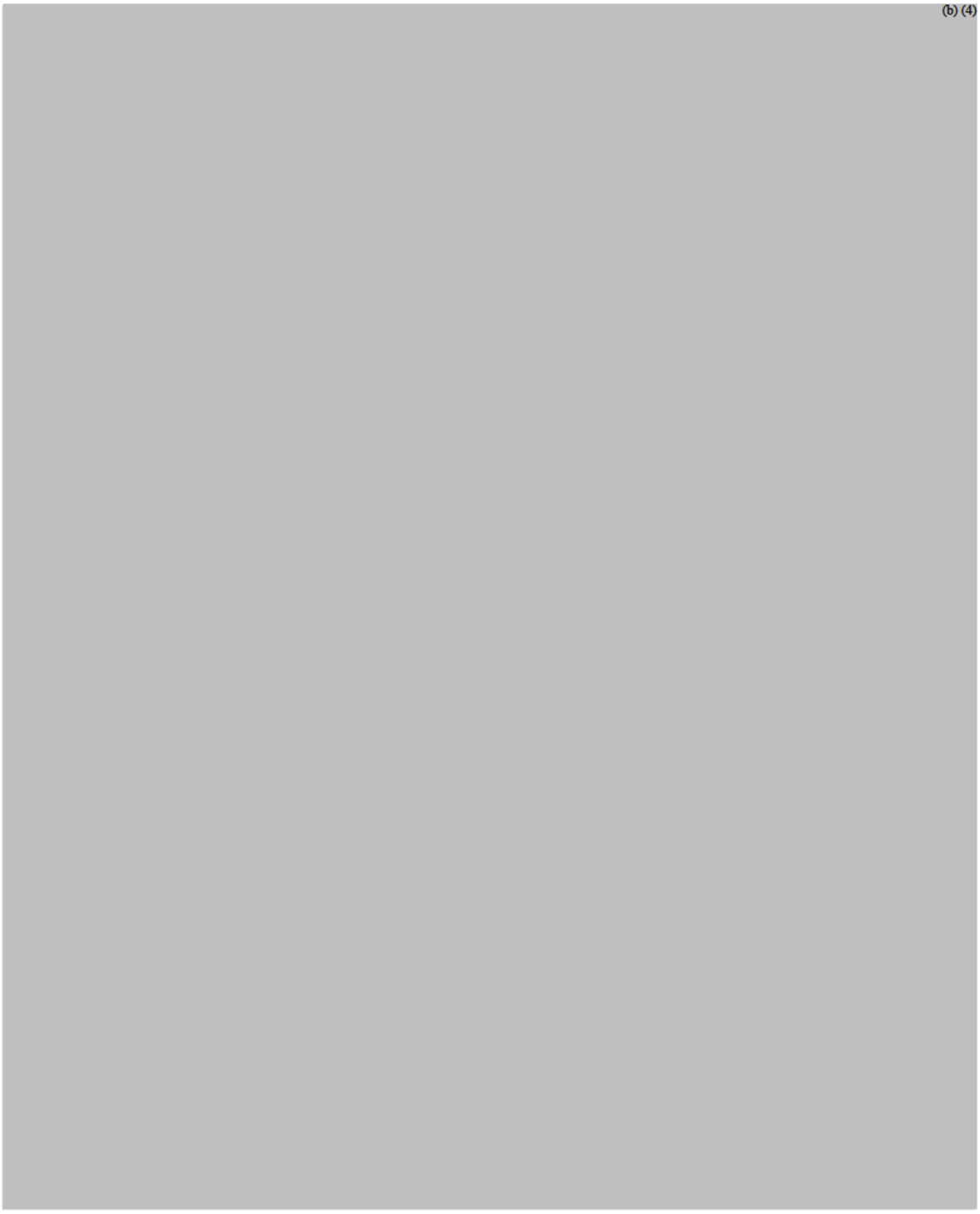
A brief overview of the manufacture of the drug product is summarized in the diagram below.

(b) (4)™ Capsules

Noven Therapeutics, LLC

High-level Manufacturing Process Flow Diagram

(b) (4)



DISSOLUTION METHOD

The dissolution method that is being proposed as a quality control tool for paroxetine mesylate capsules is summarized below:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
Paroxetine Mesylate	Capsule	II (paddle) with wire sinkers	75	simulated gastric fluid (pH 1.20 ± 0.05)	900 mL

DISSOLUTION METHOD DEVELOPMENT

There NDA did not contain dissolution method development and the following IR was requested dated 09-NOV-2012:

Provide a dissolution method development report in the NDA including the following information:

- ***Solubility data for the drug substance covering the pH range.***
- ***Detailed description of the dissolution method and the developmental parameter (equipment/apparatus selection, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions etc.) used to select the most appropriate method. The testing conditions used for each test should be clearly specified.***
- ***The complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time.***
- ***Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as validation data for the dissolution method and analytical method.***

The Applicant responded on 12-DEC-2012 referencing their approved NDA 21-299 (Pexeva® tablets) for most of the requested information. They provided some additional data to support the selection of the proposed dissolution method. The comprehensive data (from both NDAs) are reviewed under various sub-sections below.

(b) (4)

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Photostability Study I (Capsules without and with blisters)

Dissolution at (b) (4) for Capsules without blisters
Batch 1 (n=6) = (b) (4) (Mean=96%)
Batch 2 (n=6) = (b) (4) (Mean=79%)

Dissolution at (b) (4) for Capsules with blisters
Batch 1 (n=6) = 9 (b) (4) (Mean=99%)
Batch 2 (n=6) = (b) (4) (Mean=7%)

Photostability Study II (Capsules packaged in paperboard blister card, with and without paperboard carton)

Dissolution at (b) (4) for Capsules without paperboard carton
Batch 1 (n=6) = (b) (4) (Mean=98%)
Batch 2 (n=6) = (b) (4) (Mean=97%)

Dissolution at (b) (4) for Capsules with a paperboard carton
Batch 1 (n=6) = (b) (4) (Mean=95%)
Batch 2 (n=6) = (b) (4) (Mean=95%)

As seen from the highlighted data above, capsules that were exposed to light without the paperboard blister card showed slowing of dissolution for a few samples. This proved the ability of the dissolution method to pick up differences occurring in the formulation.

➢ ***Reviewer's Comments:*** *The photostability data support that dissolution method is capable of differentiating between products impaired due to external conditions. The Applicant was requested via teleconference (on 25-APR-2013) to submit the complete dissolution profiles for the photostability study to understand the changes in dissolution profiles at earlier time points. The Applicant responded on 26-APR-2013 (via email) stating that only single-point sampling at (b) (4) was done during the photo-stability dissolution study. The reviewer accepted the Applicant's response as even at the submitted (b) (4) dissolution data, the discriminating ability of the dissolution method is evident. Though the complete dissolution profile was desired, it is not essentially required to support the discriminating ability of the dissolution method.*

DISSOLUTION ACCEPTANCE CRITERIA

The following dissolution acceptance criterion was originally proposed by the Applicant as a QC for the release of paroxetine mesylate capsules:

Dissolution Acceptance Criterion
Q= (b) (4)

To support the above criterion, the following data from the Phase 3 clinical batch and the three registration/stability batches were provided:

Table 5. Dissolution Test Results for Paroxetine (as Mesylate) Capsules, 7.5 mg

	% Dissolved				
	Phase 2	**Phase 3**	**Registration/Stability**		
Time Point	**Batch 432207**	**Batch 439462**	**Batch 444141[a]**	**Batch 444252[a]**	**Batch 444253[a]**
					(b) (4)

As seen from the data above, a dissolution acceptance criterion of Q= (b) (4) is (b) (4). The data support the selection of Q= (b) (4) at 20 mins.

Reviewer's Recommended Dissolution Acceptance Criteria

The following dissolution acceptance criterion is recommended as a QC for release and on stability for paroxetine mesylate capsules **but has not yet been agreed upon by the Applicant**:

Dissolution Acceptance Criteria
Q= (b) (4) at 20 mins

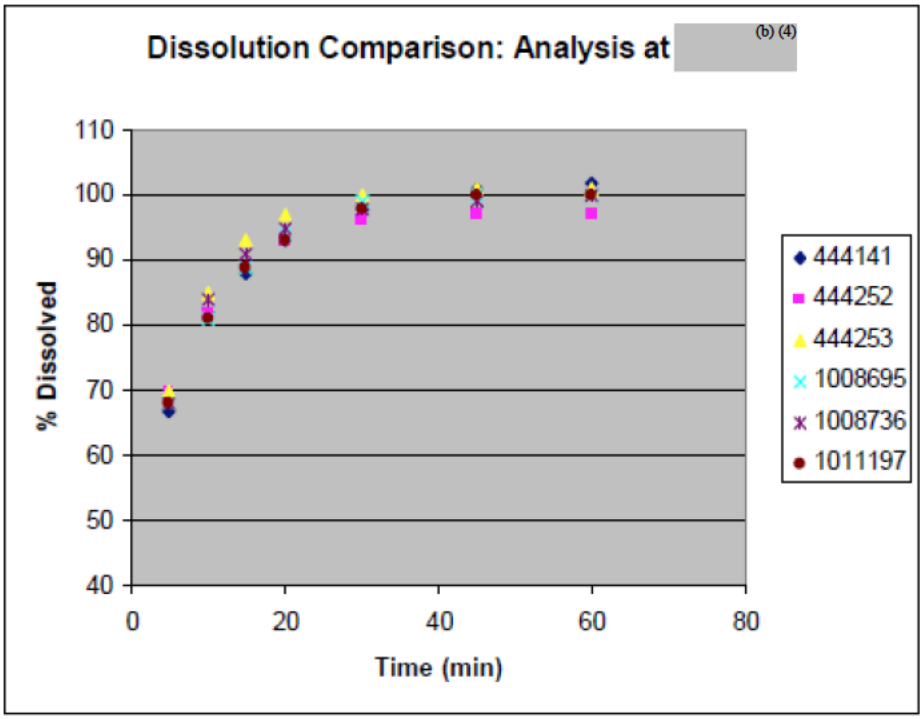
➢ ***Reviewer's Comments:*** *The Applicant was requested via teleconference (on 25-APR-2013) to (b) (4) the dissolution acceptance criterion to Q= (b) (4) at 20 mins. An agreement has not yet been reached and a response is awaited.*

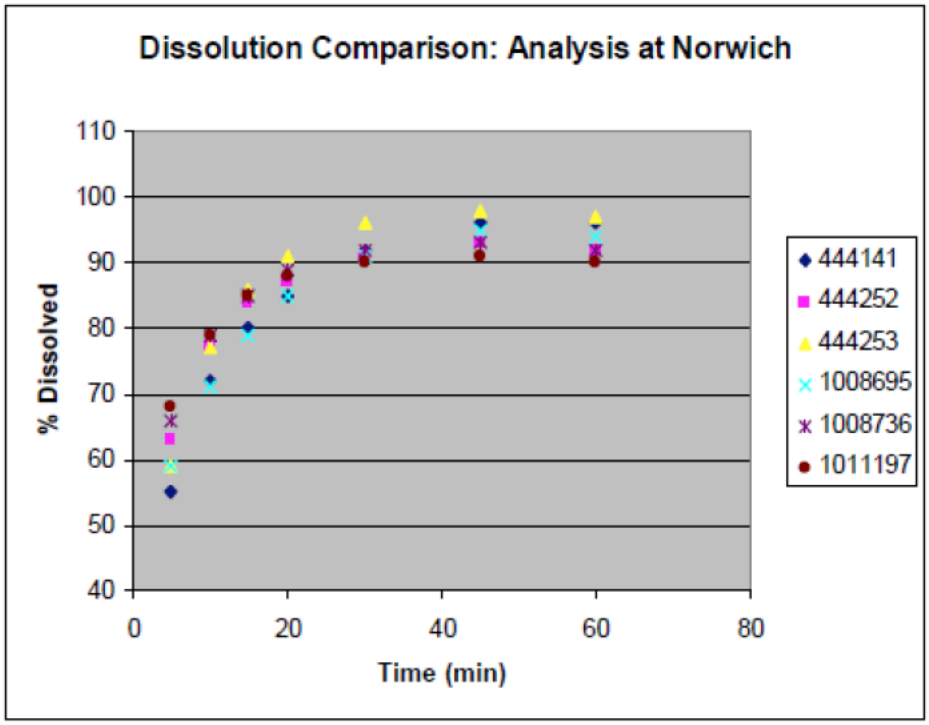
USE OF DISSOLUTION TO SUPPORT TWO DRUG PRODUCT MANUFACTURING SITES

The Applicant has contracted two drug product manufacturers for its paroxetine mesylate capsules, 7.5 mg (paroxetine mesylate capsules) product. Both sites will be routinely used as the drug product manufacturing sites. The two manufacturers are:

Norwich Pharmaceuticals, Inc. (Norwich)
6826 State Highway 12
Norwich, NY 13815
and
(b) (4)

In order to compare drug product manufactured at each of the two manufacturing sites, three batches of drug product from each of the manufacturing sites were compared head-to-head using the proposed dissolution conditions. The dissolution profiles of the six batches were then collected at each site, as shown below. The Applicant reported that the primary difference between the two sites is that the drug substance is routinely prescreened at Norwich while no routine prescreening is performed or anticipated at (b) (4)





The Applicant submitted the following f2 calculations (shown below) to support the sameness of the drug products manufactured at the two sites:

Table 6. Similarity (f2) and Difference (f1) Factors for the Mean Values as Collected at Each of the Two Manufacturing Sites.

Analysis Site	**f_1**	**f_2**
Dissolution Analyzed at Norwich	2[a]	78[a]
Dissolution Analyzed at (b) (4)	1[b]	94[b]

[a] = Calculated using only first 4 dissolution time points, because dissolution is greater than (b) (4) following the 4th time point

[b] = Calculated using only first 3 dissolution time points, because dissolution is greater than (b) (4) following the 3rd time point

➢ ***Reviewer's Comments:*** *The reference used for the above f2 analyses is the dissolution data from the other site, for e.g., the reference for the (b) (4) dissolution data is the data from the Norwich site. Since the clinical batch was manufactured at the Norwich site, the reviewer reanalyzed the f2 calculation for (b) (4) site by using the mean dissolution values of the Phase 3 clinical batch and the primary stability batches as the reference (data from Table 5). f2>50 was observed supporting the use of (b) (4) site along with Norwich site for drug product manufacturing.*

CONCLUSIONS

From the Biopharmaceutics perspective an APPROVAL recommendation for NDA 204-516 for (b) (4) (paroxetine mesylate) Capsules cannot be granted as of April 26, 2013 due to the pending agreement on the recommended dissolution acceptance criterion.

The acceptable dissolution method and recommended acceptance criterion for the paroxetine mesylate capsules are:

Drug Name	**Dosage Form**	**USP Apparatus**	**Speed (rpm)**	**Medium**	**Volume (mL)**	**Acceptance Criterion**
Paroxetine Mesylate	Capsule	II (paddle) with wire sinkers	75	simulated gastric fluid (pH 1.20 ± 0.05)	900 mL	Q= (b) (4) at 20 minutes

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEEPIKA LAKHANI
04/26/2013

SANDRA SUAREZ
04/26/2013