CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209501Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 209501
Review #1

Drug Name/Dosage Form	LYRICA® CR (proposed)(Pregabalin)Extended Release Tablets
Strength	82.5, 165, 330 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer Inc.
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	OPQ/ONDP/DNDPAPI/BII
Drug Product	Chris Hough	OPQ/ONDP/DNDPII/BIV
Process	Shujun Chen/Haitao Li	OPQ/OPF/DPAII/BVI
Microbiology		
Facility	Christina Capacci-Daniel	OPQ/OPF/DIA/BII
Biopharmaceutics	Kelly Kitchens/Sandra Suarez	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead	Caryn McNab/Michael Tollon	
Environmental Analysis (EA)		

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, biopharmaceutics, process, microbiology, facilities, and drug product, CMC recommends the approval of LYRICA CR 82.5 mg, 165 mg, 330 mg extended release tablets.

II. Summary of Quality Assessments

A. Product Overview

LYRICA CR 82.5 mg, 165 mg, and 330 mg film coated extended release tablets is designed for once daily administration with a proposed indication for neuropathic pain associated with diabetic peripheral neuropathy, postherpectic neuralgia, and fibromyalgia. The safety and efficacy of these proposed indications are under review by the clinical division.

The applicant provides a right of reference for NDA 21-446 for the pregabalin drug substance which was approved on 12/30/2014. Most of the API information for pregabalin is found in NDA 21-466. Dr. Debasis Ghosh, the drug substance reviewer states "The specification for Pregabalin is the same as previously provided in Lyrica® (Pregabalin) Capsules C-V NDA 21-446, (b) (4) specification. (b) (4) The applicant provided batch analysis data for three batches which were used for the development, clinical and stability studies. In addition, Certificate of Analysis for two more recent Pregabalin batches used for the manufacture of commercial scale development batches of all three strengths of tablets were provided. Based on Certificate of Analysis, the retest date is (b) (4)

LYRICA CR extended release tablets are almond-shaped tablets with different film coating colors to distinguish the three dosage strengths of 82.5 mg, 165 mg, and 330 mg. The 82.5 mg tablet is a light blue film coated almond-shape, debossed with "Pfizer" on one side and "PGN 82.5" on the other. The 165 mg tablet is a beige film coated almond-shape, debossed with "Pfizer" on one side and "PGN 165" on the other. The 330 mg tablet is a rose film coated almond-shape, debossed with "Pfizer" on one side and "PGN 330" on the other. The proposed commercial tablets utilize (b) (4) The 82.5 mg, 165 mg and 330 mg tablet core compositions are qualitatively the same, using the same excipients,

stability batches of pregabalin extended release tablets are packed in high-density polyethylene bottles and closures with induction seal liners. The expiration date of 30 months for products packaged in high density polyethylene (HDPE) bottles with induction seal (b) (4) is granted with a storage statement "Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted between 15 °C and 30 °C (between 59 °F and 86 °F)."

B. Special Product Quality Labeling Recommendations (NDA only) – N/A

C. Final Risk Assessment (see Attachment)

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters	L	-	N/A	-

	• Scale/equipment • Site				
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

Administrative

A. Reviewer's Signature

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
Application Technical Lead
ONDP/DIVII/Branch IV

NDA 209501
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Reviewer's Assessment: *Adequate*

3.2.P.8 Stability

3.2.P.8.1 Summary of stability studies and Conclusion.

In accordance with ICH guideline Q1A(R2), a registration stability program consisting of pregabalin extended release 82.5 mg, 165 mg and 330 mg tablets packaged in HDPE bottles [redacted] has been completed through 36 months at the long term storage conditions of 25 °C/60 % RH and 6 months at the accelerated storage condition of 40 °C/75 evaluated in accordance with ICH guideline Q1B. Three batches of each strength (82mg, 165mg and 330mg) packaged in [redacted] 30-count [redacted] HDPB bottle configuration [redacted] were placed on stability.

The registration stability batches were made at [redacted]% of the proposed commercial scale and were packaged at Pfizer Freiburg, Germany, the proposed commercial site.

The stability samples were evaluated for appearance, assay and degradation products as well as dissolution, [redacted] and microbiological quality. The data from the registration stability study demonstrate that there are no significant trends in any of the measured parameters except for the specified degradation product [redacted]. Based on ICH Q1E guideline, statistical analyses was performed on the 36-month stability data for assay, [redacted] content, total degradation [redacted]. Increasing trends in [redacted] are confirmed to be statistically significant (p-values < [redacted]) for all lots under different package and storage conditions. With respect to a [redacted] specification of NMT [redacted]%, the 36-month stability data support a shelf life of 30 months.

[redacted], unspecified degradation products, total degradation products and dissolution. [redacted] and there is no indication of any significant degradation through 36 months of storage, therefore it is considered acceptable.

Conclusions for Expiration Period, Storage, and Labeling

Based on the 36 month stability data for three batches the proposed expiration dating is 30 months for product packaged in high density polyethylene (HDPE) bottles with induction seal [redacted] and stored as discussed below.

Storage Conditions

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

Storage Conditions and Testing Frequency

The stability protocol design for the registration stability tablet batches, including storage conditions and sample times, is as follows:

Table 3.2.P.8.1-5. Stability Protocol - Three batches of each strength

	Interval (Months)							
	0	3	6	9	12	18	24	36
Initial	A							
40°C/75%RH		B	B					
25°C/60%RH		B	B	B	A	B	A	A
5°C		C	C	C	C	C	C	C

Tests to be applied in accordance with the above protocol include:

A: Appearance, Assay, Degradation Products, Dissolution*, [redacted] (b) (4) Microbial Testing (TAMC, TYMC)

B: Appearance, Assay, Degradation Products, Dissolution*, [redacted] (b) (4)

[redacted] (b) (4)

* Dissolution method changed during registration stability program [redacted] (b) (4). Other dissolution conditions unchanged. [redacted] (b) (4) [redacted] Dissolution without sinkers performed at 12 months, 24 months and 36 months.

Photostability

A photostability study was conducted on one batch of each strength according to ICH Guideline Q1B.

Consistent with Option 2, one batch of each strength was exposed to simulated sunlight, receiving total visible illumination of 1.2 million lux hours and integrated near ultraviolet energy of 200 watt hours/square meter. A dark control sample was covered and placed in the light cabinet alongside the unpackaged test sample. Both the dark control and the unpackaged test sample were exposed to the following:

- UV light to achieve a total minimum exposure of 200 watt hours/meter^2.
- Fluorescent light to achieve a total minimum exposure of 1.2 million lux hours.

The unprotected samples and foil wrapped dark control samples were tested for appearance, assay, degradation products, [redacted] (b) (4) dissolution [redacted] (b) (4)

Reviewer's Assessment: *Stability studies were conducted as per ICH Q1A(R2),B. There was a change made in the Dissolution studies-* (b) (4)

The 36-months of data provided for all strengths and all configurations supports a 30month expiry.

3.2.P.8.2 Post-approval protocol and stability commitments:

POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

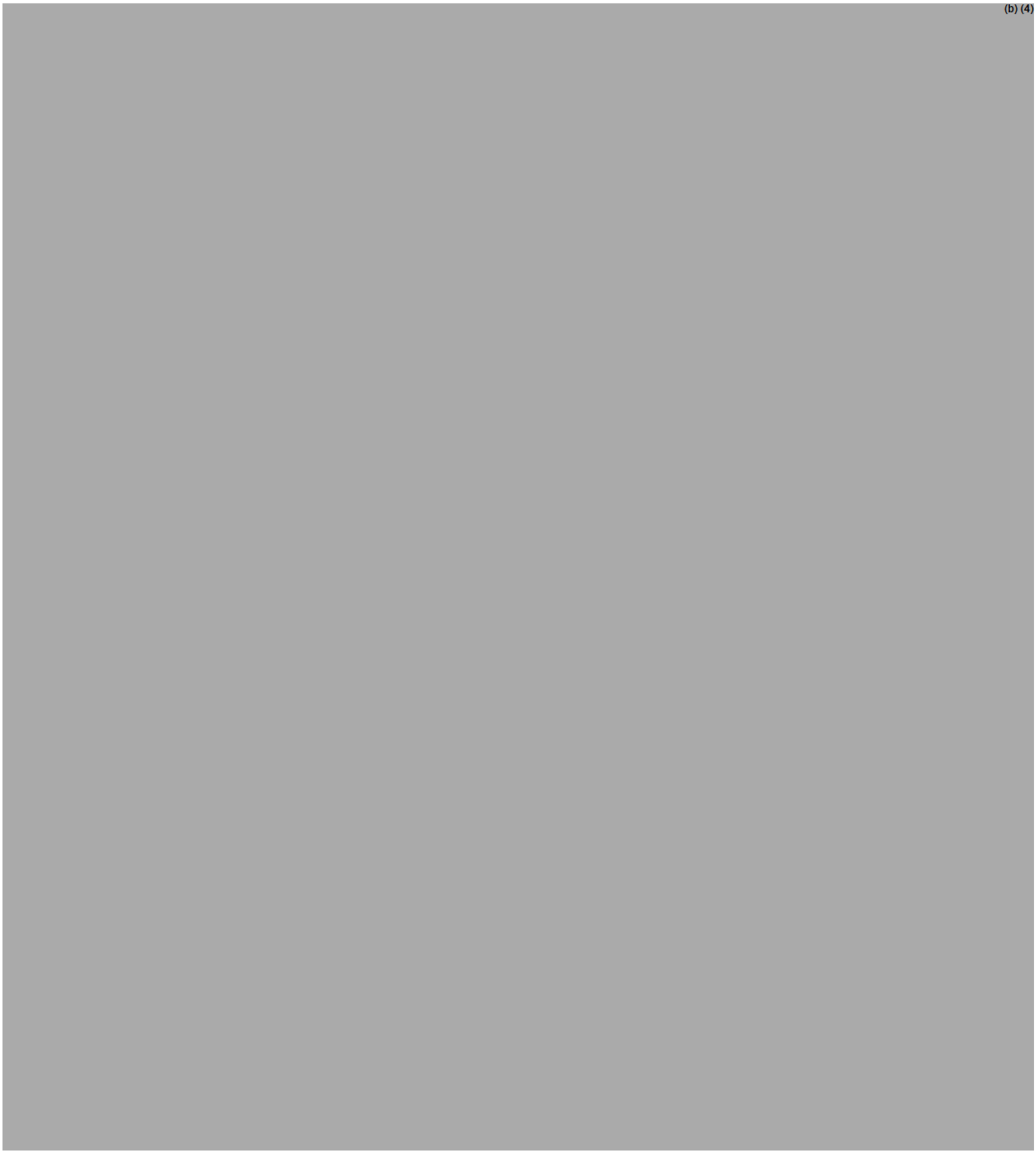
Post-Approval Stability Protocol and Commitment to Confirm Shelf Life

The first three commercial scale batches of drug product manufactured will be placed on stability in accordance with the protocol in Table 3.2.P.8.2-1. Samples will be stored in HDPE bottles (b) (4) at the stability conditions indicated.

(b) (4)

Annual production batches will be selected at a rate of at least one batch per year per strength (assuming adequate production) for stability testing per the protocol below for the first three commercial batches.

(b) (4)



Post-Approval Stability Protocol and Commitment : ***Adequate.*** *The post-approval stability protocol and commitment is acceptable.*

R Regional Information

Environmental Analysis

Reviewer's Assessment: The Sponsor, Pfizer Global Research and Development claims categorical exemption from an environmental assessment of the basis of 21 CFR 25.31 (a) and (2).

Methods Verification Package

Reviewer's Assessment: N/A

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

Primary Drug Product Reviewer Name and Date: Christopher J. Hough, Ph.D., 14-Aug.-2017.

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

CHAPTER IV: Labeling

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LABELING

R Regional Information

1.14 Labeling

Immediate Container Label- Sample: 1:1 size

(b) (4)

Reviewer's Assessment: No container closures for samples were proposed by the Sponsor, but the label is presented.

Bottle label, 82.5 mg strength 1:1 size:

Bottle label, 165 mg strength 1:1 size:

Bottle label, 330 mg strength 1:1 size:

Carton Labeling: N/A

Reviewer's Assessment:

Labeling of the immediate container is adequate

List of Deficiencies:

The Physician's Insert should have a clear description of the tablet in the Description section (section 11). The following sentences is suggested: LYRICA CR extended release tablets are almond-shape film-coated tablets colored light-blue, beige, or rose depending on their strength and debossed with "Pfizer" on one side and "PGN" with its strength on the other.

Primary Labeling Reviewer Name and Date: Christopher Hough, Ph.D.

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

Christopher Hough

Digitally signed by Christopher Hough
Date: 9/13/2017 05:23:37PM
GUID: 508da7220002a180df90e5ffe899ce1f

Julia Pinto

Digitally signed by Julia Pinto
Date: 9/13/2017 05:13:41PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Pregabalin Extended Release (ER) Tablets, 82.5 mg, 165 mg, and 330 mg, under the 505(b)(1) path. The drug product is indicated for neuropathic pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN) [redacted] (b) (4). Pregabalin ER tablets have been developed to support once daily (QD) administration following an evening meal.

NDA: 209501

Drug Product Name / Strength: LYRICA® CR (proposed), 82.5, 165, 330 mg

Route of Administration: Oral

Applicant Name: Pfizer Inc.

Review Summary:

The Applicant proposes to use the same dissolution method that was previously approved for the immediate release capsule product. The Applicant adequately justified the dissolution method parameters for the proposed extended-release tablet product. Dissolution data submitted support the proposed dissolution acceptance criteria. The Applicant's proposed dissolution acceptance criteria are acceptable on an interim basis; an additional specification time point at 9 hours will be recommended to ensure quality control from 55% to complete release. The Applicant will be requested to submit dissolution data (at release and stability) at 1 hour, 4 hours, 9 hours and 24 hours, and propose dissolution acceptance criteria at each of these time points.
Therefore, the following comments will be conveyed to the Applicant:

In order to have a better quality control of your product, we believe an additional dissolution time point at 9 hours is necessary. Following the approval of the NDA, we recommend that you submit dissolution data (at release and stability) for all the batches at 1 hour, 4 hours, 9 hours and 24 hours. We also recommend that you propose acceptance criteria at each time point for the Agency to review and make a final decision on the dissolution acceptance criteria for future batches.

[redacted] (b) (4)

In vitro alcohol interaction studies demonstrate that there is no evidence of pregabalin dose dumping in the presence of alcohol.

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

From the Biopharmaceutics perspective, NDA 209501 for Pregabalin Extended-Release Tablets is recommended for **approval.**

List Submissions being reviewed (table):

Date of Submission	Purpose of Submission
December 15, 2016	Original
May 31, 2017	Response to CMC information request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

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

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ADEQUATE

Dissolution Method:

The proposed dissolution method is described in the following table, and is the same method that is approved for Pregabalin immediate release capsules:

Table 3.2.P.2.2-23. Proposed Dissolution Method for Pregabalin ER Tablets

Dissolution Medium	0.06 N HCl
Volume	900 mL
Temperature	37°C
Apparatus	USP apparatus 2 (Paddles)
Agitation Rate	50 rpm

Selection of medium, apparatus, and agitation rate

- Pregabalin solubility is > 30 mg/ml in pH range 1-13 at room temperature. Pregabalin is classified as being highly soluble per the Biopharmaceutics Classification System (BCS).

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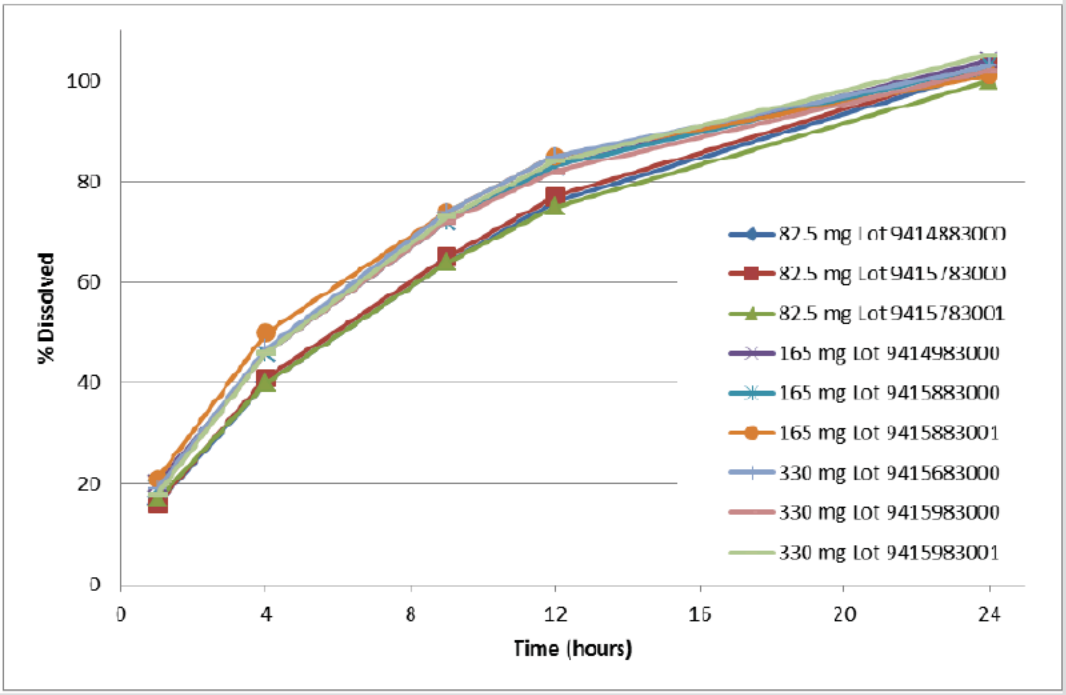
Figure 3.2.P.2.2-17. Dissolution Profiles (Mean of N=6) for Pregabalin ER 82.5 mg (Formulation D1005611), 165 mg (Formulation D1005612) and 330 mg (Formulation D1005613) Tablets



- **The dissolution method is adequate.**

Acceptance Criteria:

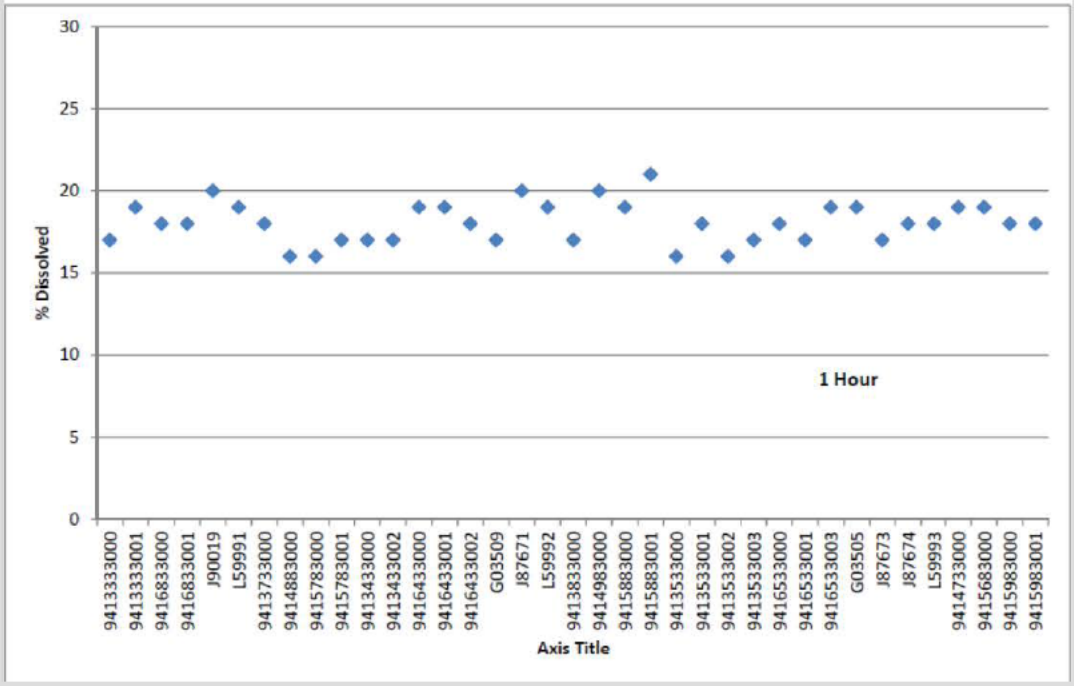
- The Applicant proposed the following dissolution acceptance criteria:
  1 hour: (b) (4) %
  4 hours: (b) (4) %
  24 hours: (b) (4) %
- The following table and figures summarize the dissolution batch release and registration stability data for a total of 10 batches of 82.5 mg, 12 batches of 165 mg and 15 batches of 330 mg tablets:

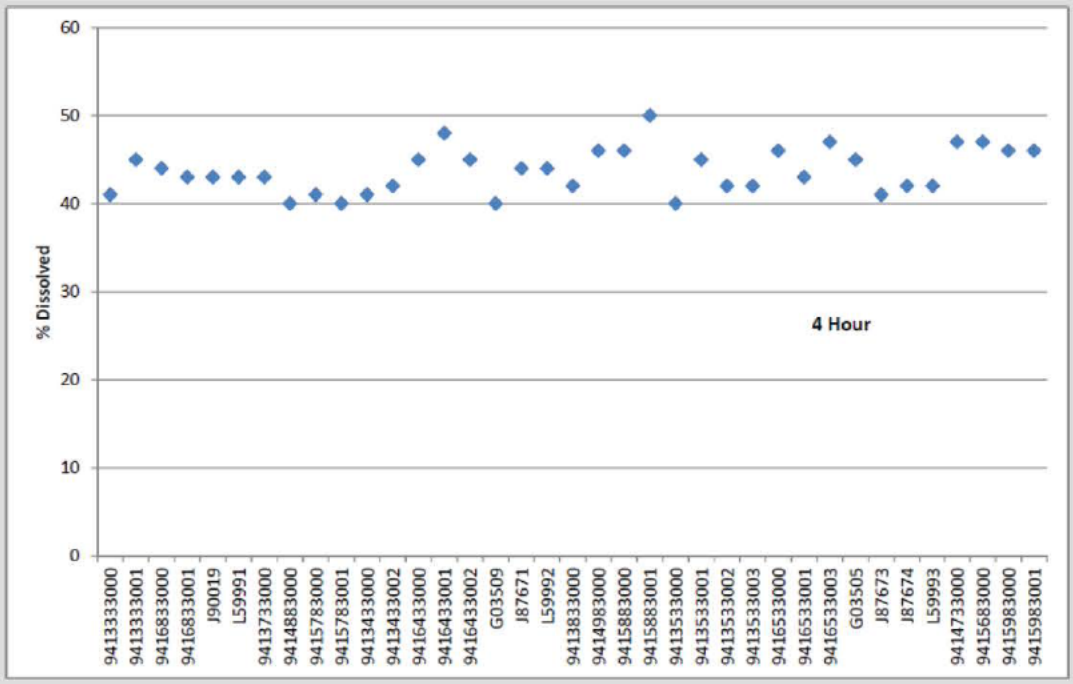
Table 3.2.P.5.6-9. Summary of Ranges Observed for Dissolution at Release

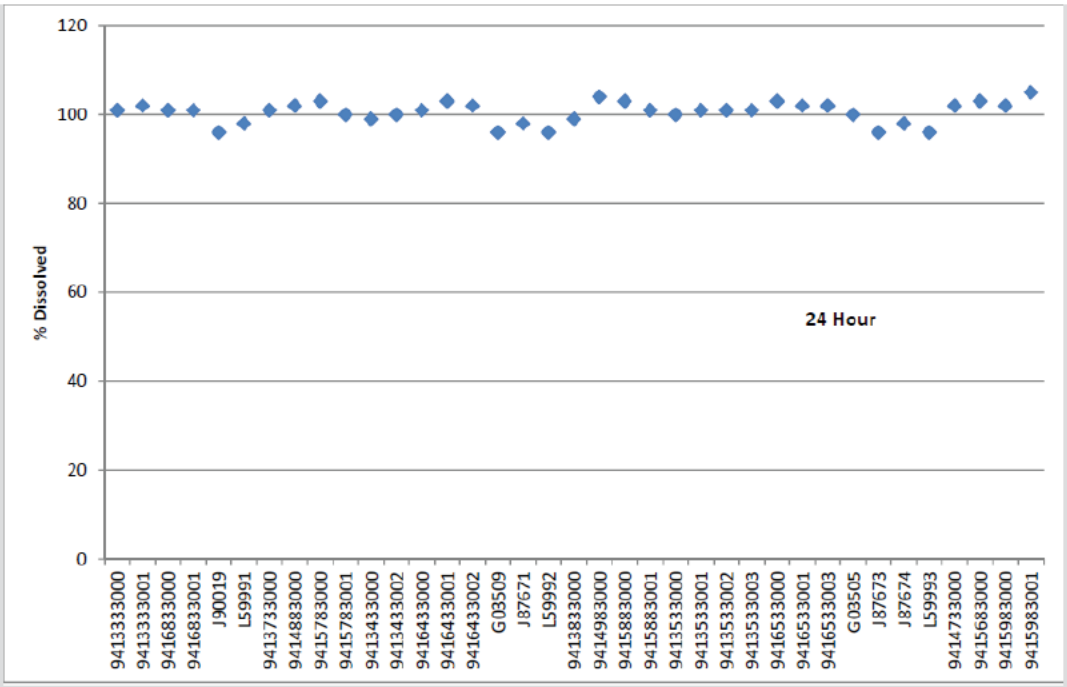
Dissolution Results	82.5 mg, 165 mg and 330 mg Tablets[1]
1 hour	
Overall Mean (%)	18
Range of Mean Values (%)	16-21
Range of Individual Values (%)	14-24
4 hours	
Overall Mean (%)	44
Range of Mean Values (%)	40-50
Range of Individual Values (%)	36-54
24 hours	
Overall Mean (%)	101
Range of Mean Values (%)	96-105
Range of Individual Values (%)	85-107

[1] Based on testing for 10 batches of 82.5 mg, 12 batches of 165 mg and 15 batches of 330 mg tablets.

Figure 3.2.P.5.6-2. Mean Dissolution Values for Pregabalin ER Tablets at 1 Hour, 4 Hours and 24 Hours







- Although the Applicant submitted mean and range dissolution values for the clinical and registration stability batches, the Applicant has not submitted complete dissolution data. Therefore, the Applicant was requested to submit the complete dissolution profile data (individual, mean, %CV, and profiles) at release and for the primary stability batches of the drug product in the 74-day letter dated February 22, 2017. This IR was reiterated to the Applicant on May 15, 2017:

  Provide the complete dissolution profile data (individual, mean, %CV, and profiles) at release and for the primary stability batches of your drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).

  On May 31, 2017, the Applicant responded as follows:

  The primary stability batches for pregabalin ER tablets are listed in Table 5. The dissolution profiles for the primary stability batches were provided in Figure 3.2.P.2.2-17 of the NDA and are also provided below in Figure 2. Dissolution was performed using USP apparatus 2 (paddles) at 50 RPM and 37 °C with 900 mL of 0.06 N hydrochloric acid as the dissolution medium. Complete dissolution profile data (individual values, mean values, %CV values) for the primary stability batches are provided in Table 6 to Table 8.

  (b) (4)

  (b) (4) *The proposed dissolution method without sinkers was used to test 9 month 5°C samples from the primary stability batches in lieu of release data. This is the data provided in Figure 2 and Table 6 to Table 8 and supports the proposed dissolution acceptance criteria.*

Table 5. Primary stability batches for pregabalin ER tablets

Strength	Formulation Identification	Lot Number
82.5 mg	D1005611	9414883000
		9415783000
		9415783001
165 mg	D1005612	9414983000
		9415883000
		9415883001
330 mg	D1005613	9415683000
		9415983000
		9415983001

Figure 2. Dissolution Profiles (Mean of N=6) for Pregabalin ER 82.5 mg (Formulation D1005611), 165 mg (Formulation D1005612) and 330 mg (Formulation D1005613) Tablets

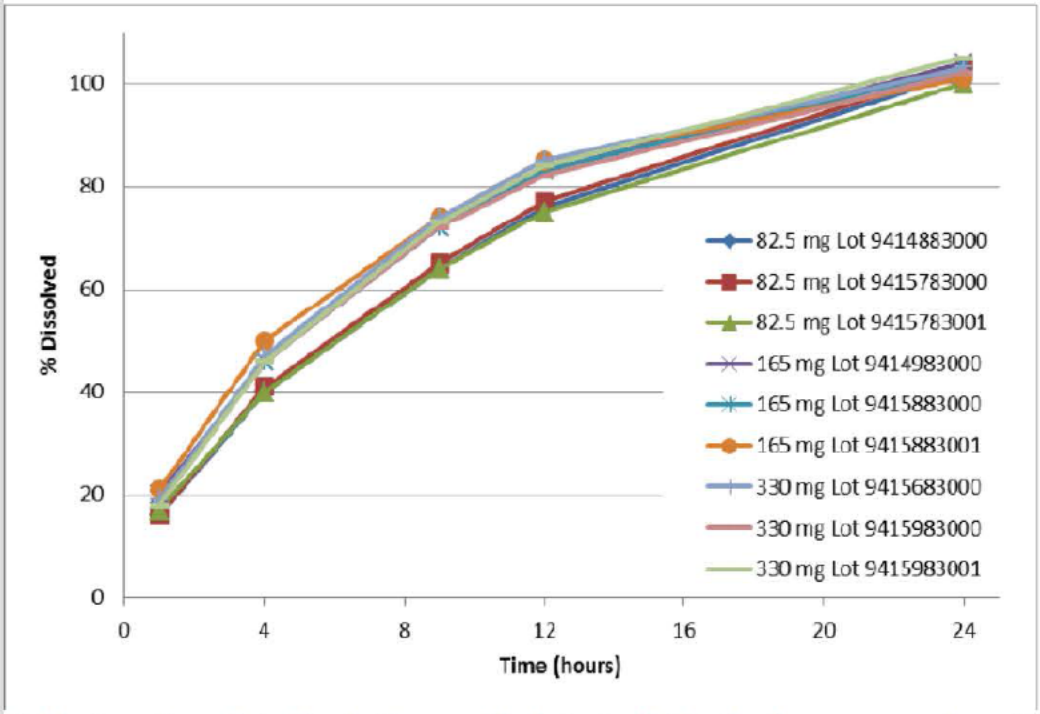


Table 6. Complete dissolution profile data (individual values, mean values, %CV values) for the primary stability batches of 82.5 mg pregabalin ER tablets

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
82.5	9414883000	1	15	40	64	75	103
		2	17	40	64	76	104
		3	17	41	64	75	103
		4	17	42	67	79	104
		5	16	39	65	76	99
		6	15	38	62	74	99
		Mean	16	40	64	76	102
		%CV	6.1	3.5	2.5	2.3	2.3
		Range	15-17	38-42	62-67	74-79	99-104

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
82.5	9415783000	1	17	43	66	78	106
		2	19	43	67	81	103
		3	15	40	64	76	102
		4	18	43	69	81	105
		5	15	39	62	73	102
		6	15	37	62	74	101
		Mean	17	41	65	77	103
		%CV	10.7	6.3	4.4	4.4	1.9
		Range	15-19	37-43	62-69	73-81	101-106

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
82.5	9415783001	1	20	45	70	82	102
		2	16	37	63	74	98
		3	18	40	64	75	101
		4	17	40	64	75	102
		5	16	38	60	71	97
		6	17	38	62	74	101
		Mean	17	40	64	75	100
		%CV	8.7	7.2	5.3	4.9	2.1
		Range	16-20	37-45	60-70	71-82	97-102

Table 7. Complete dissolution profile data (individual values, mean values, %CV values) for the primary stability batches of 165 mg pregabalin ER tablets

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
165	9414983000	1	19	45	72	83	104
		2	20	48	74	85	103
		3	19	44	69	81	102
		4	18	45	72	83	103
		5	19	46	72	82	104
		6	22	49	75	86	105
		Mean	20	46	72	83	104
		%CV	7.1	4.2	2.9	2.2	1.0
		Range	18-22	44-49	69-75	81-86	102-105

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
165	9415883001	1	23	53	77	88	104
		2	22	51	76	86	103
		3	19	45	70	81	99
		4	22	49	74	84	100
		5	22	52	76	87	104
		6	21	48	72	81	99
		Mean	22	50	74	85	102
		%CV	6.4	5.9	3.7	3.6	2.4
		Range	19-23	45-53	70-77	81-88	99-104

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
165	9415883000	1	19	45	72	83	105
		2	19	49	75	86	105
		3	18	47	72	84	103
		4	19	46	71	83	102
		5	18	43	67	79	101
		6	19	48	73	84	103
		Mean	19	46	72	83	103
		%CV	2.8	4.7	3.7	2.8	1.6
		Range	18-19	43-49	67-75	79-86	101-105

Table 8. Complete dissolution profile data (individual values, mean values, %CV values) for the primary stability batches of 330 mg pregabalin ER tablets

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
330	9415683000	1	22	49	76	87	104
		2	24	52	81	89	103
		3	17	44	71	83	101
		4	17	46	72	83	104
		5	17	45	71	82	101
		6	18	48	75	85	105
		Mean	19	47	74	85	103
		%CV	16.0	6.2	5.2	3.2	1.6
		Range	17-24	44-52	71-81	82-89	101-105

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
330	9415983000	1	20	47	74	83	102
		2	19	47	73	82	101
		3	18	49	73	84	104
		4	16	43	67	79	101
		5	17	44	69	80	99
		6	19	49	73	83	104
		Mean	18	47	72	82	102
		%CV	8.1	5.4	3.9	2.4	1.9
		Range	16-20	43-49	67-74	79-84	99-104

Dose	Lot	#	1 Hr	4 Hrs	9 Hrs	12 Hrs	24 Hrs
330	9415983001	1	18	48	75	86	105
		2	18	46	72	84	105
		3	18	46	74	85	104
		4	19	47	75	85	105
		5	18	45	71	83	107
		6	18	44	72	83	104
		Mean	18	46	73	84	105
		%CV	2.2	3.1	2.4	1.4	1.0
		Range	18-19	44-48	71-75	83-86	104-107

- The complete dissolution data support the Applicant's proposed dissolution acceptance criteria.

  1 hour: (b) (4) %
  4 hours: (b) (4) %
  24 ours: (b) (4) %

- However, an additional specification time point at 9 hours will be recommended to ensure quality control from 55% to complete release. The Applicant will be requested to submit dissolution data (at release and stability) at 1 hour, 4 hours, 9 hours and 24 hours, and propose dissolution acceptance criteria at each of these time points.
- **The dissolution acceptance criteria are acceptable on an interim basis.**

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

Reviewer's Assessment: ADEQUATE

- A study was conducted to evaluate the effect of alcohol on in vitro dissolution of pregabalin ER tablets. Alcohol concentrations of 0%, 5%, 20%, and 40% v/v were studied.
- One lot each of 82.5 mg and 330 mg pregabalin ER film coated tablets (Formulation ID D0904827 and D0904940) were tested using the proposed commercial dissolution method conditions, where the dissolution media were prepared from mixing various concentrations (0%, 5%, 20%, and 40%) of ethanol with the proposed commercial method medium of 0.06 N HCl. Since all 3 tablet strengths are designed to have similar dissolution profiles (see Module 2.3.P.2 Pharmaceutical Development), the 165 mg strength was not tested.
- Dissolution was tested with n=12 dosage units in each medium. Dissolution samples were collected every 15 minutes for 2 hours and two additional samples were taken at 4 hours and 8 hours for comparative purposes.
- The dissolution profile data are summarized in the following figures for the 82.5 mg and 330 mg strengths:

Figure 3.2.P.2.2-18. Mean Drug Dissolved Profiles for 82.5 mg Pregabalin ER Tablets in 0.06N HCl and in 0.06N HCl with Various Concentrations of Ethanol

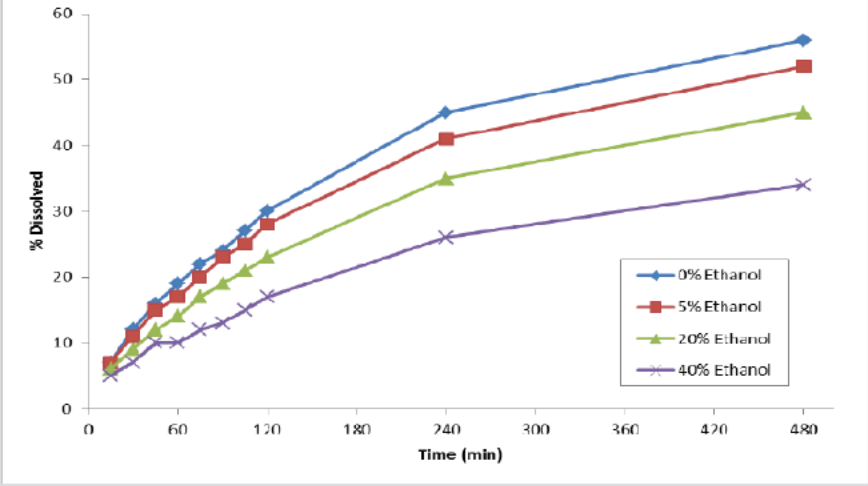
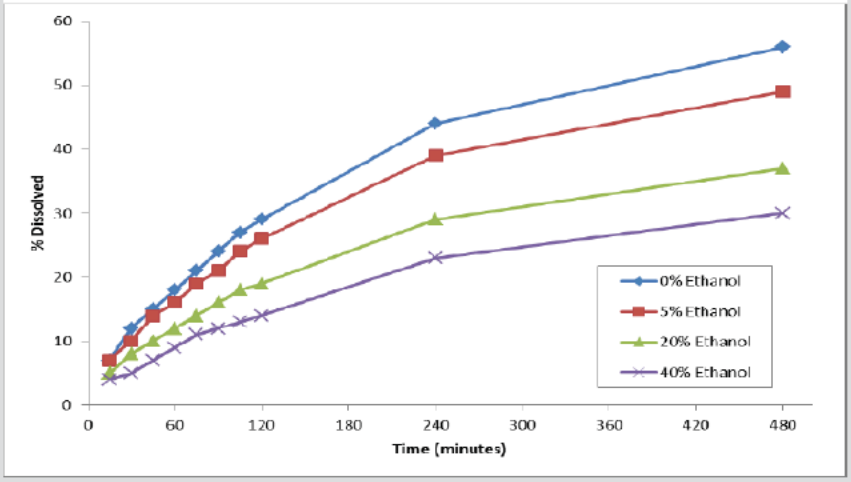


Figure 3.2.P.2.2-19. Mean Drug Dissolved Profiles for 330 mg Pregabalin ER Tablets in 0.06N HCl and 0.06N HCl with Various Concentrations of Ethanol



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

Strength	% EtOH (v/v)	F2
82.5 mg	0% vs. 5%	80.37
	0% vs. 20%	59.50
	0% vs. 40%	45.35
330 mg	0% vs. 5%	72.66
	0% vs. 20%	50.32
	0% vs. 40%	42.50

- The f2 values greater than 50 indicate the dissolution profiles with 0% Ethanol are similar to profiles with 5% and 20% Ethanol. Although the f2 values for 40% Ethanol indicate that the dissolution profiles with 0% Ethanol are not similar to profiles with 40% Ethanol, the dissolution is slower in 40% Ethanol compared to 0% Ethanol.
- **Therefore, the in vitro alcohol interaction studies suggest that there is no evidence of alcohol dose dumping.**

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: ADEQUATE

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

1. *The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.*
   - Dissolution testing of the drug product using the proposed dissolution method with 0.06 N HCl, and using pH 4.5 acetate buffer and pH 6.8 phosphate buffer, did not show any evidence of in vitro dose dumping. The drug product also did not show evidence of in vitro dose dumping in various concentrations of alcohol (see the above (see the above ***Dissolution Method and Acceptance Criteria*** section).

- The median Tmax of a single 330 mg ER dose administered following an evening meal was 8 to 10 hours (range 4 to 16 hours). The mean and range of observed Cmax and AUC values were similar across a variety of evening meals including a high calorie, high fat meal (see the following Table 2.7.1.71 and Figure 2.7.1.17).
- The median Tmax of a single 330 mg ER dose administered fasted in the evening occurred at 5 to 6 hours post-dose. Cmax was approximately 15% lower and AUC approximately 23-30% lower relative to pregabalin ER administered with food (see the following Table 2.7.1.71 and Figure 2.7.1.17).

Table 2.7.1.71. Descriptive Summary of Plasma Pregabalin PK Results Following Single Dose of Pregabalin 330 mg ER Tablets and Pregabalin 300 mg IR Capsules: Studies A0081188, A0081227, A0081228, A0081238 and A0081239

Study (A008)	Treatment[a,b]	*N*, *n*	AUC_{inf}[c] (µg.h/mL)	C_{max}[c] (µg/mL)	T_{max}[c] (h)	$t_{½}$[c] (h)
Evening Administration						
1227	ER, low-fat, evening	28, 28	60.8 (16)	3.7 (18)	10.0 (5.0–12.0)	6.7 (17)
	ER, med-fat, evening	28, 27	60.1 (15)	3.6 (18)	10.0 (8.0–16.0)	6.6 (17)
	ER, high-fat, evening	27, 27	57.6 (16)	3.6 (19)	10.0 (6.0–16.0)	6.5 (18)
	IR, med-fat, evening	27, 27	59.1 (12)	5.4 (19)	4.0 (2.0–6.0)	6.3 (18)
1228	ER, med-kcal, evening	24, 24	50.8 (21)	3.1 (16)	8.0 (4.0–12.1)	6.7 (14)
	ER, fasted, evening	23, 23	35.5 (36)	2.6 (25)	5.0 (1.0–12.1)	7.5 (18)
	IR, fasted, evening	23, 23	58.0 (14)	6.7 (22)	1.5 (0.67–4.0)	6.4 (14)
1238	ER, low kcal, evening	23, 23	54.4 (25)	3.4 (19)	8.0 (5.0–12.0)	6.9 (16)
	ER, med kcal, evening	24, 24	54.4 (22)	3.4 (19)	8.0 (4.0–12.0)	6.9 (16)
	ER, fasted, bedtime[d]	22, 21	42.2 (32)	2.9 (26)	6.0 (3.0–8.0)	7.5(15)
	IR, fasted, evening	22, 22	61.9 (16)	6.4 (21)	1.5 (0.67–6.0)	6.6 (17)
Morning Administration						
1239	ER, low kcal, morning	23, 23	40.2 (33)	2.7 (22)	5.0 (4.0–12.0)	7.2 (17)
	ER, med kcal, morning	23, 23	46.3 (34)	2.7 (23)	8.0 (4.0–12.0)	7.0 (19)
	ER, high kcal, morning	24, 24	53.4 (22)	2.8 (19)	12.0 (4.0–16.0)	6.7 (17)
	IR, fasted, morning	23, 23	54.0 (16)	6.3 (24)	1.5 (0.67–2.0)	6.7 (18)
Lunch (Midafternoon) Administration						
1188	ER, low kcal, mid-day	25, 24	47.5 (28)	2.9 (20)	6.0 (4.0–16.0)	7.0 (16)
	ER, med kcal, mid-day	26, 24	51.3 (28)	3.2 (26)	6.0 (5.0–10.0)	6.9 (12)
	ER, high kcal, mid-day	28, 26	51.0 (24)	3.1 (21)	8.0 (4.0–16.0)	7.0 (15)
	IR, fasted, mid-day	27, 26	54.9 (16)	6.9 (29)	1.5 (0.67–4.0)	6.5 (15)

Med=medium; kcal=kilocalorie; N=number of participants in the treatment group, n=number of participants included in the analysis

[a] Pregabalin ER was administered at a dose of 330 mg. Pregabalin IR was administered at a dose of 300 mg

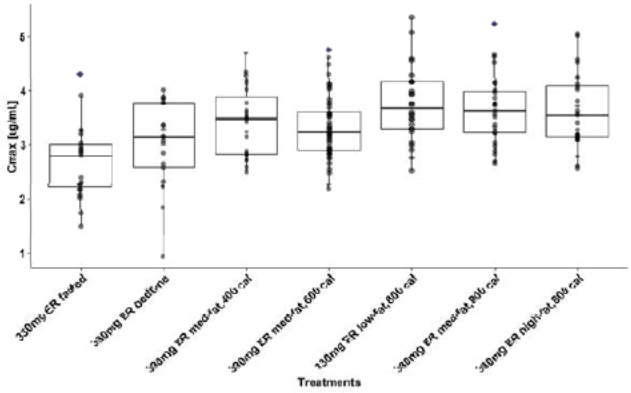
[b] Accompanying meals were categorized by either calorie or fat content. Low kcal = 400 – 500 calories/meal, med kcal = 600 – 750 calories/meal, and high kcal = 800–1000 calories/meal (in each instance with 30 % of calories coming from fat). Low-fat = 15 % fat content, med-fat = 30 % fat content, and high-fat = 50 % fat content (in each instance with a meal of 800 – 1000 calories)

[c] Values are expressed as geometric mean (% coefficient of variation) for AUC_{inf} and C_{max}, median (range) for T_{max}, and arithmetic mean (% coefficient of variation) for $t_{½}$

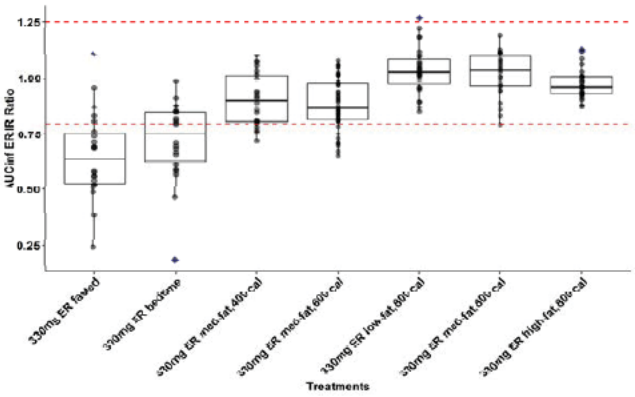
[d] Pregabalin was administered approximately 4 h after the (medium kcal) evening meal.

Figure 2.7.1.17 **Box and Whisker Plots of Observed C_{max} for Single Dose of Pregabalin ER 330 mg Tablets (Panel a) and AUC_{inf} Ratio of Single Dose of Pregabalin ER 330 mg Tablets to Pregabalin IR 300 mg Capsules (Panel b) Across Studies A0081227, A0081228, and A0081238**

a. C_{max}



b. AUC_{inf} ER:IR ratio



2. *The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.*
   - Pregabalin ER tablets administered QD (82.5, 165, 330, 660 mg/day) following the evening meal had equivalent AUC24 compared to pregabalin IR capsules administered fasted BID or TID (75, 150, 300, 600 mg/day) (see the following Table 2.7.1.68).
   - Degree of fluctuation (PTF) with ER tablets was approximately 35% lower than with IR administered fasted BID and approximately 8% lower than IR capsules administered fasted TID (see the following Table 2.7.1.68).

Table 2.7.1.68. Descriptive Summary of Plasma Pregabalin Pharmacokinetics from Multiple Dose Studies A0081198, A0081215, A0081216, A0081225, and A0081226

Dose	Study (A008)	N	Parameters[a,b] AUC_{24} (µg.h/mL)	Overall C_{max} (µg/mL)	Overall T_{max} (h)	Overall C_{min} (µg/mL)	PTF	AUC_{tau}^1 AUC_{tau}^2 AUC_{tau}^3 (µg.h/mL)			C_{max}^1 C_{max}^2 C_{max}^3 (µg/mL)			C_{min}^1 C_{min}^2 C_{min}^3 (µg/mL)		
Preliminary Multiple Dose Study Evaluating the PK and Relative BA of 330 mg Pregabalin ER Administered Once Daily Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12h without Food																
1 x 330 mg ER q24h	1225[c]	20	55.2 (21)	3.97 (18)	8.0 (5.0-12.1)	0.69 (39)	1.40 (20)	---	---	---	---	---	---	---	---	---
150 mg IR q12h	1225[c]	20	27.9 (18)[b]	4.08 (20)	1.51 (0.667-4.0)	1.02 (28)	1.30 (18)	---	---	---	---	---	---	---	---	---
Multiple Dose Studies Evaluating the PK, Relative BA, and Dose Proportionality of Proposed Commercial Pregabalin ER Tablets Administered Once Daily Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12h or TID without Food																
25 mg IR TID	1215	17	15.2 (16)	1.2 (12)	12.7 (1.0-13.0)	0.31 (24)	1.44 (20)	7.34 (17)	3.98 (16)	3.90 (16)	1.1 (13)	1.2 (15)	0.85 (15)	0.31 (25)	0.31 (24)	0.42 (21)
1 x 82.5 mg ER q24h	1215	18	14.7 (18)	1.0 (16)	8.0 (5.0-10.0)	0.20 (30)	1.33 (17)	---	---	---	---	---	---	---	---	---
75 mg IR q12h	1226	24	31.5 (18)	3.2 (21)	12.7 (0.7-13.5)	0.59 (25)	1.95 (22)	15.3 (18)	16.2 (18)	---	2.4 (20)	3.1 (21)	---	0.59 (25)	0.62 (24)	---
2 × 82.5 mg ER q24h	1226	23	30.0 (19)	2.0 (20)	8.0 (4.0-11.9)	0.43 (27)	1.27 (14)	---	---	---	---	---	---	---	---	---
1 x 165 mg ER q24h	1226	24	29.4 (17)	2.0 (17)	8.0 (5.0-11.9)	0.44 (24)	1.26 (13)	---	---	---	---	---	---	---	---	---
150 mg IR q12h	1198	24	62.1 (15)	6.4 (20)	12.7 (0.7-13.5)	1.11 (21)	2.01 (22)	30.3 (15)	31.9 (15)	---	4.54 (20)	6.4 (20)	---	1.15 (20)	1.15 (23)	---
2 × 165 mg ER q24h	1198	22	59.3 (17)	4.1 (16)	10.0 (5.0-12.0)	0.82 (25)	1.32 (13)	---	---	---	---	---	---	---	---	---
1 x 330 mg ER q24h	1198	22	60.1 (18)	4.2 (20)	10.0 (5.0-11.9)	0.85 (26)	1.33 (15)	---	---	---	---	---	---	---	---	---
300 mg IR q12h	1216	18	120.0 (13)	11.4 (17)	12.7 (0.7-14.0)	2.08 (22)	1.83 (22)	57.9 (12)	62.1 (14)	---	9.3 (18)	11.1 (19)	---	2.11 (21)	2.37 (20)	---
2 × 330 mg ER q24h	1216	18	115.5 (14)	7.8 (12)	9.0 (6.0-12.0)	1.76 (26)	1.24 (11)	---	---	---	---	---	---	---	---	---

BA=bioavailability; N=number of subjects who received treatment and contributed to PK analyses; q12h=every 12 h; q24h=every 24 h; TID=every 6-6-12 h (e.g., 7 AM, 1 PM, 7 PM)

[a] For A0081225, PK parameters were assessed across the 0–12-h interval for pregabalin IR and 0–24-h interval for pregabalin ER. For all other studies, parameters were assessed across the 0–24-h interval for both pregabalin ER and IR. Serial PK sampling started 48 h following the first dose for A0081225 and 72 h following the first dose for the remaining studies. Evening dose (ER and IR) was administered at 0 h and morning dose (IR) at 12 h and afternoon dose at 18 h (IR for A0081215 only). PK parameters 1, 2, 3 are for each IR dosing interval beginning with the evening dose.

[b] Geometric mean (%CV) was calculated for all parameters except for T_{max} (median [range]).

[c] Summary of proposed commercial pregabalin ER tablets only (Table 2.7.1.1).

- Steady-state Cmax of ER tablets administered QD following the evening meal is approximately 10-17% and 30-36% lower than Cmax with evening and morning fasted IR capsules administration, respectively (see the following table 2.7.1.69).
- Steady-state Cmin of ER tablets administered QD following the evening meal is approximately 15-27% lower than Cmin of IR administered fasted BID and 36% lower than IR capsules administered fasted TID (see the following table 2.7.1.69).

Table 2.7.1.69. Statistical Summary of Treatment Comparisons: Pregabalin ER Tablets QD Versus Pregabalin IR Capsules BID or TID [Studies: A0081198, A0081215, A0081216, A0081225, and A0081226]

Study (A008)	Study Design	Pregabalin Dose (mg)		ER/IR Ratio (90% CIs)[a,b]		
		ER	IR	AUC	C_{max}	C_{min}
Preliminary Multiple Dose Study Evaluating the PK and Relative BA of 330 mg Pregabalin ER Administered Once Daily Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12h without Food						
1225[c]	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 330 q24h	1 x 150 q12h	99.03 (95.27, 102.94)	97.26 (91.44, 103.45)	67.89 (62.50, 73.74)
Multiple Dose Studies Evaluating the PK, Relative BA, and Dose Proportionality of Proposed Commercial Pregabalin ER Tablets Administered Once Daily Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12h or TID without Food						
1215	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 82.5 q24h	1 x 25 TID	96.02 (92.84, 99.30)	82.19 (77.05, 87.67)	63.71 (59.20, 68.56)
1226	ER: 600 kcal, med-fat, evening IR: Fasted, evening	2 x 82.5 q24h	1 x 75 q12h	95.21 (92.52, 97.97)	63.79 (61.00, 66.71)	73.32 (69.27, 77.62)
	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 165 q24h	1 x 75 q12h	93.05 (90.47, 95.71)	62.62 (59.92, 65.43)	74.15 (70.11, 78.41)
1198	ER: 600 kcal, med-fat, evening IR: Fasted, evening	2 x 165 q24h	1 x 150 q12h	94.56 (92.05, 97.14)	63.84 (60.82, 67.00)	73.32 (69.24, 77.63)
	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 330 q24h	1 x 150 q12h	97.30 (94.71, 99.95)	66.15 (63.02, 69.42)	78.08 (73.74, 82.67)
1216	ER: 600 kcal, med-fat, evening IR: Fasted, evening	2 x 330 q24h	1 x 300 q12h	96.29 (92.35, 100.41)	68.34 (63.76, 73.24)	84.44 (74.49, 95.33)

CI=confidence interval; med-fat=medium fat (30%); kcal=kilocalorie; q12h=every 12 h; q24h=every 24 h; TID=every 6-6-12 h (e.g., 7 AM, 1 PM, 7 PM)

[a] For A0081225, pregabalin ER AUC/2 to allow for comparison with pregabalin IR AUC over 12 hours. For A0081225, PK parameters were assessed across the 0 – 12-h interval for pregabalin IR and 0–24 h interval for pregabalin ER. For all other studies, parameters were assessed across the 0 – 24-h interval for both pregabalin ER and IR. Serial PK sampling started 48 h following the first dose for A0081225 and 72 h following the first dose for the remaining studies.

[b] The ratios (and 90% CIs) were expressed as percentages.

[b c] Summary of proposed commercial pregabalin ER tablets only (Table 2.7.1.1).

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

- Two ER tablets administered concurrently QD following the evening meal are bioequivalent (AUC and Cmax) to one ER tablet of the same dose (e.g., 2 x 82.5 mg vs. 1 x 165 mg; 2 x 165 mg vs. 1 x 330 mg) (see the following Table 2.7.1.70).

Table 2.7.1.70. Statistical Summary of Treatment Comparisons: One or Two Tablets of Pregabalin ER Administered QD [Studies: A0081198 and A0081226]

Study (A008)	Study Design[a]	Pregabalin ER Dose (mg)		Ratio (90% CIs)[b, c]		
		Test	Ref	AUC_{24}	C_{max}	C_{min}
Multiple Dose Studies Evaluating Proposed Commercial Pregabalin ER Tablets						
1126	ER: 600 kcal, med-fat, evening	2 x 82.5 q24h	1 x 165 q24h	102.31 (99.43, 105.28)	101.87 (97.42, 106.53)	98.89 (93.42, 104.68)
1198	ER: 600 kcal, med-fat, evening	2 x 165 q24h	1 x 330 q24h	97.19 (94.56, 99.89)	96.51 (91.87, 101.38)	93.90 (88.59, 99.54)

CI=confidence interval; ER=extended release; kcal=kilocalorie; med-fat=medium fat (30%); q24h=every 24 h

[a] The ratios (and 90% CIs) were expressed as percentages.

- Within subject and between subject variability for AUC and Cmax is low (< 25%) for pregabalin ER administered following the evening meal (see the following Table 2.7.1.73).

Table 2.7.1.73. Variability Estimates (%CV) for Pregabalin ER Tablet C_{max} and AUC in Healthy Volunteers

Study (A008)	Pregabalin ER Treatments[a]	Intrasubject Variability (%CV)		Intersubject Variability (%CV)	
		AUC[a]	C_{max}	AUC[a]	C_{max}
Multiple Dose Studies					
Evening Meal					
1198	2x165 mg, 600 kcal, med-fat, evening 1x330 mg, 600 kcal, med-fat, evening	5.5	5.7	18.4	19.4
1226	2x82.5 mg, 600 kcal, med-fat, evening 1x165 mg, 600 kcal, med-fat, evening	6.0	5.9	15.4	17.4
Single Dose Studies					
Evening Meal					
1227	1x330 mg, 800 kcal, low-fat, evening 1x330 mg, 800 kcal, med-fat, evening 1x330 mg, 800 kcal, high-fat, evening	7.1	8.8	13.6	15.7
1238	1x330 mg, 400 kcal, med-fat, evening 1x330 mg, 600 kcal, med-fat, evening	9.5	7.0	23.2	17.8
IVIVC Study (Evening Meal)					
1309	1x82.5 mg (dose-normalized), 600 kcal, med-fat, evening 1x330 mg (dose-normalized), 600 kcal, med-fat, evening	9.2	5.9	14.7	16.0
Morning Administration					
1239	1x330 mg, 400 kcal, low-fat, breakfast 1x330 mg, 600 kcal, med-fat, breakfast 1x330 mg, 800 kcal, high-fat, breakfast	20.4	11.5	23.7	14.5
Lunch (Midafternoon) Administration					
1188	1x330 mg, 400 kcal, med-fat, lunch 1x330 mg, 600 kcal, med-fat, lunch 1x330 mg, 800 kcal, med-fat, lunch	12.7	8.4	26.1	20.0

%CV=coefficient of variation; AUC=area under the plasma PK profile from time 0 to 24 h for multiple dose or from time 0 extrapolated to infinite time for single dose; kcal=kilocalorie

[a] Only pregabalin ER treatments administered following a meal were used in calculation of %CV. Low-fat = 15 % fat content, med-fat = 30 % fat content, and high-fat = 50 % fat content

Source: 1188, Table 16.1.9.2; 1198, 16.1.9.2; 1226, 16.1.9.2; 1227, 16.1.9.2; 1238, 16.1.9.2; 1239, 16.1.9.2.2; 1309, 16.1.9.2.3.

4. *The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product* (**Reviewer's Note:** this is not a CFR criterion; this criterion is set forth by the Division of Biopharmaceutics).
   - The proposed Pregabalin ER tablets will be administered QD (once a day), whereas the approved Pregabalin IR capsules are administered BID (twice a day) or TID (three times a day).

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

Bridging of Formulations

Reviewer's Assessment: N/A

Since the clinical formulations used in pivotal BE studies A0081198, A0081215, A0081226 are similar to the commercial formulations (see **Module 2.3.P.2** Pharmaceutical Development), bridging studies are unnecessary.

Biowaiver Request

Reviewer's Assessment: N/A

- The Applicant conducted PK study no. A0081309 on the 330 mg and 82.5 mg strengths. They compared the exposure of all strengths across studies, and claim the product has dose-proportional PK. However, the Applicant did not conduct a dose-proportionality study; therefore, dose-proportionality cannot be concluded.
- The following IR was conveyed to Applicant in the 74-day letter dated February 22, 2017, and reiterated in the May 15, 2017 IR letter:

Elaborate on the basis of approval for the strengths not included in pivotal BA/BE studies with supporting data. Note that in the absence of in vivo dose proportionality/BE studies to support the approval of the strengths not included in pivotal BA/BE studies, a waiver request of the BA/BE studies should be included in the NDA submission. It is noted that a BE study with the higher and lower strengths was conducted. The approval of the intermediate strength may be approved on the basis of a biowaiver request and using the bracketing approach provided the following data are submitted:

a. The proposed lower and higher strengths of your product have the same dosage form;
b. The lower and higher strength products have the same manufacturing process; and
c. Dissolution profile comparisons between the intermediate strength with the lower and higher strengths in three different media meet the similarity requirements (i.e. F2 >50 for all the strengths).

- The Applicant submitted the following response in an email dated May 18, 2017:

Pfizer's rationale for the basis of approval of the intermediate strength (165 mg) is as follows:

- *Per agreement between Pfizer and the Agency at the End of Phase 2 meeting (08 September 2008 meeting minutes) the pivotal BA/BE studies were conducted as multiple dose studies. The clinical data presented in Module 2.7.1 (Summary of Biopharmaceutics), Table 2.7.1.70 demonstrated bioequivalence in vivo for 2x82.5 mg versus 1x165 mg (study A0081226) and 2x165 mg versus 1x330 mg (study A0081198). Individual, median, and quartiles for dose-normalized Cmax and AUC overlapped for the three tablet strengths 82.5, 165, and 330 mg (Figure 2.7.1.16, Studies A0081198, A0081215, A0081216, A0081226). The proposed commercial formulations as described in Table 2.7.1.6 were used in each of the four studies noted above.*
- *Study A0081309 evaluated single dose 82.5 mg (lower strength) and single dose 330 mg tablets (higher strength) (Section 2.7.1.2.4.1). This study demonstrated bioequivalence of the dose normalized Cmax and AUC exposures for the 82.5 mg and 330 mg tablets, thereby supporting the conclusions from the BA/BE studies noted above. The proposed commercial formulations as described in Table 2.7.1.6 were also used in this study.*

Given the available in vivo evidence that the dose proportionality for the intermediate tablet strengths is adequately demonstrated, it was Pfizer's assumption that the agreement/studies mentioned above would be acceptable in lieu of a formal biowaiver request.

Pfizer would like to confirm that the above mentioned rationale and data submitted in our NDA can be utilized for approval of the 165mg strength in lieu of submitting a biowaiver request.

- Since the Office of Clinical Pharmacology is responsible for evaluating the BA/BE studies, the clinical pharmacology reviewer, Dr. Srikanth Nallani, was consulted to determine if the Applicant's rationale is adequate. Dr. Nallani indicated that the BA/BE studies are adequate (see the Clinical Pharmacology review by Dr. Srikanth Nallani).
- Therefore, the Applicant's rationale for the basis of approval of the 165 mg strength is adequate.

List of Deficiencies:
There are no additional deficiencies. However, the following comments will be conveyed to the firm:

In order to have a better quality control of your product, we believe an additional dissolution time point at 9 hours is necessary. Following the approval of the NDA, we recommend that you submit dissolution data (at release and stability) for all the batches at 1 hour, 4 hours, 9 hours and 24 hours. We also recommend that you propose acceptance criteria at each time point for the Agency to review and make a final decision on the dissolution acceptance criteria for future batches.

Primary Biopharmaceutics Reviewer Name and Date:
Kelly M. Kitchens, Ph.D., August 22, 2017

Secondary Reviewer Name and Date:
Haritha Mandula, Ph.D., September 9, 2017

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 9/08/2017 10:21:38AM
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Kelly Kitchens

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Date: 9/06/2017 03:50:39PM
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