

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211675Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211675

Review #1

Drug Name/Dosage Form	Upadacitinib extended release tablets
Strength	15 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Original</i>	<i>18-DEC-2018</i>	<i>All</i>
<i>Amendment</i>	<i>12-FEB-2019</i>	<i>Drug substance, drug product</i>
<i>Amendment</i>	<i>07-MAR-2019</i>	<i>Drug product</i>
<i>Amendment</i>	<i>09-APR-2019</i>	<i>Drug substance</i>
<i>Amendment</i>	<i>12-APR-2019</i>	<i>Drug product</i>
<i>Amendment</i>	<i>15-APR-2019</i>	<i>Drug substance</i>
<i>Amendment</i>	<i>26-APR-2019</i>	<i>Drug product</i>
<i>Amendment</i>	<i>09-MAY-2019</i>	<i>Drug product</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sam Bain	Donna Christner
Drug Product	Valerie Amspacher	Craig M. Bertha
Process	Pratibha Bhat	Joanne Wang
Microbiology	Pratibha Bhat	Joanne Wang
Facility	Pratibha Bhat	Joanne Wang
Biopharmaceutics	Rajesh Savkur	Haritha Mandula/Sandra Suarez
Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	Michael Chasey
Environmental	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III	[REDACTED]	(b) (4)	Active	N/A	Sufficient information in NDA
	III			Active	N/A	Sufficient information in NDA
	III			Active	N/A	Sufficient information in NDA

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

DOCUMENT	APPLICATION #	DESCRIPTION
IND	114717	upadacitinib for rheumatoid arthritis (RA), (b) (4)
IND	[REDACTED]	[REDACTED] (b) (4)
IND	[REDACTED]	[REDACTED]
IND	[REDACTED]	[REDACTED]
IND	[REDACTED]	[REDACTED]

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

N/A

II. Summary of Quality Assessments

A. Product Overview

The drug product Upadacitinib Extended-Release Tablets (15 mg) (b) (4)

The chiral upadacitinib is a weakly basic compound (pKa of 4.7) and is said to be a selective Janus kinase (JAK) 1 inhibitor and have high solubility and permeability. Note that the chirality is introduced by a stereospecific hydrogenation using a chiral Ruthenium catalyst. The extended-release (ER) tablet is (b) (4)

The dosage form is manufactured (b) (4)

The container closure system (CCS) is a 3 oz. (b) (4) bottle (b) (4)

 Total Number of Comparability Protocols (ANDA only)

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	15 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The active component of the Upadacitinib ER Tablet drug product is a novel oral selective reversible Janus kinase 1 inhibitor. It has been evaluated in Phases 1, 2, and 3 clinical trials in healthy subjects and adult patients with moderately to severely active rheumatoid arthritis (RA), either alone or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (DMARDs). Clinical studies were conducted under IND 114717. The Applicant developed the

product in three strengths 7.5 mg, 15 mg and 30 mg. However, only the 15 mg strength is intended for marketing.

Upadacitinib drug substance is manufactured (b) (4)

The OND pharmacology/toxicology review team has evaluated 35 impurities in terms of safety and did not have any concern with the controls imposed by the applicant.

The applicant has tightened the drug substance assay requirements to more closely reflect their historical data. The applicant has revised the application (b) (4)

The applicant has a retest period of (b) (4) months for the drug substance when stored at less than (b) (4) °C, which is acceptable.

The manufacturing process for Upadacitinib ER Tablets consists of (b) (4)

The proposed commercial batch size and batch formula is same as that of SQBs. The equipment to be used for commercial batches has the same design, size and operating principles as the equipment used for the submitted site-specific stability/qualification batches (SQBs). In process control acceptance criteria are either maintained the same as that for the SQBs or have been tightened for better control. The overall yields of the SQBs are within the acceptable limits. The hold time at each unit operation is established based on hold time study. There are no differences in manufacturing processes for the clinical and commercial batches.

The Critical Quality Attributes (CQA's) of Upadacitinib ER tablets include identity, purity, assay, uniformity of dosage units, degradation products, dissolution, (b) (4) and appearance. The applicant has also provided more detail regarding the formulation, (b) (4)

(b) (4) Based on a thorough assessment of (b) (4) the stored drug product, the applicant will not be performing microbial limits testing routinely on stability samples. The analytical method for determination of the identity, assay, and degradants related to upadacitinib in the drug product has been clarified such that repeatability and precision is assured by the system suitability requirements. The applicant has clarified that the main degradant/impurity of the upadacitinib (b) (4)

The method used to

determine impurities is adequate in its ability to detect and quantify this main upadacitinib-related degradant/impurity. Stability data provided in the application supports a **shelf-life/expiry for the drug product of 24 months**.

The Biopharmaceutics review focused on the dissolution method development, dissolution data, dissolution acceptance criteria, *in vitro/in vivo* correlation (*IVIVC*), multi-media dissolution, *in vitro* alcohol dose dumping, and extended-release designation claim.

A non-linear level A *IVIVC* model was developed and successfully validated (i.e., the model met the internal and external predictability criteria) using several ER formulations of the 30 mg strength and one formulation of the 15 mg strength. Since the *IVIVC* model was constructed and adequately validated using both the 30 mg and 15 mg strengths, the model is applicable to both strengths. Based on the Applicant's and Reviewer's analysis, the *IVIVC* model does not support wider dissolution acceptance criteria beyond $\pm 10\%$ variation around the mean. There is no significant effect of alcohol on the release profile of the product; the *in vitro* drug release profile of the drug product is similar over the pH range of 1.2 – 6.8. The Extended-Release Designation claim of the drug product has been granted since the data submitted support the requirements under 21CFR 320.25(f). The Phase 3 Clinical Trial Formulation differs from the Proposed Commercial Formulation. The Applicant has bridged the two formulations via an *in vitro* dissolution comparison and an *in vivo* BE study. Based on the submitted information, bridging of the two formulations has been adequately established and the two formulations are similar to each other. From the Biopharmaceutics perspective, this application is deemed adequate for approval.

All the facilities listed in the application are acceptable. Both the drug product and drug substance facilities are approved based on the firm's inspection history and manufacturing experience. There are also no major GMP issues raised based on the review of the submitted site-specific stability/qualification batches (SQBs).

In conclusion the CMC/OPQ recommends **approval** of the application.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA-211675-ORIG-1

Drug Product Name / Strength: Upadacitinib extended-release, 15 mg (b) (4) tablets**Route of Administration:** Oral**Applicant Name:** Abbvie**Review Summary:**

The Applicant submitted NDA-211675 under section 505(b)(1) to the Division of Pulmonary, Allergy and Rheumatology Products on 12/18/2018. In this submission, the Applicant is seeking approval of Upadacitinib extended-release, 15 mg (b) (4) tablets as an oral selective reversible JAK1 inhibitor to be indicated for the once-daily treatment in adult patients with moderately to severely active rheumatoid arthritis, either alone or in combination with methotrexate or other conventional synthetic disease modifying antirheumatic drugs. The Applicant developed the product in three strengths 7.5 mg, 15 mg and 30 mg; however, only the 15 mg is intended for marketing.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution acceptance criteria, IVIVC, multi-media dissolution, in vitro alcohol dose dumping, and extended-release designation claim.

The final dissolution method and acceptance criteria as agreed upon by the Agency and the Applicant are listed below:

Method:	In-house
Apparatus:	USP apparatus 1 (Baskets)
Medium:	50 mM Phosphate buffer pH 6.8
Volume:	900 mL
Temperature:	37 °C
Speed:	100 rpm
Time points:	1, 2, 4, 6, 8, 10, 12, 16, 20, 24 Hours
Acceptance criteria:	1 hour: (b) (4) %
	4 hours: (b) (4) %
	12 hours: NLT (b) (4) %

A non-linear level A IVIVC model was developed and successfully validated (i.e., the IVIVC model met the internal and external predictability criteria) using several ER formulations of the 30 mg strength and one formulation of the 15 mg strength. Since the IVIVC model was constructed and adequately validated using both the 30 mg and 15 mg strengths, the model is applicable to both strengths. Based on the Applicant's and Reviewer's analysis, the IVIVC model does not

support wider dissolution acceptance criteria beyond $\pm 10\%$ variation around the mean. There is no significant effect of alcohol on the release profile of the product; the in vitro drug release profile of the drug product is similar over the pH range of 1.2 – 6.8. The Extended Release Designation claim of the drug product has been granted since the data submitted support the requirements under 21CFR 320.25 (f). The Phase 3 Clinical Trial Formulation differs from the Proposed Commercial Formulation. The Applicant has bridged the two formulations via an in vitro dissolution comparison and an in vivo BE study. Based on the submitted information, bridging of the two formulations has been adequately established and the two formulations are similar to each other.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA-211675-ORIG-1, Upadacitinib extended release tablets, 15 mg, is **Adequate** for approval.

List Submissions being reviewed:

12/18/2018	NDA 211675/Original submission/Sequence 0002
04/09/2019	Response to Information Request-Quality/Sequence 0013

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

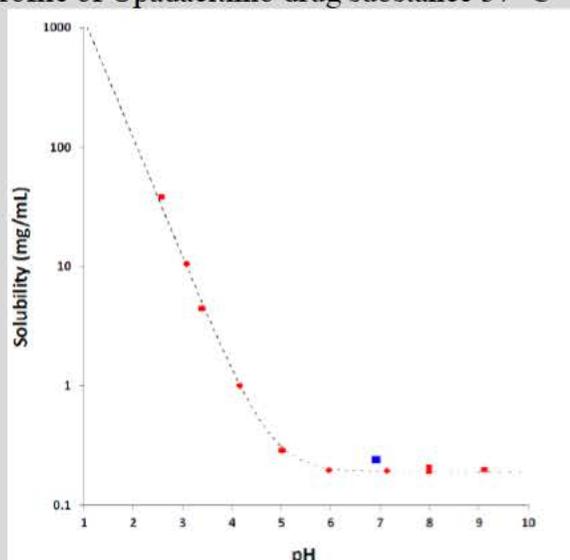
Solubility:

The hemihydrate form of Upadacitinib was used to measure the pH-solubility profile. The Applicant has stated that the minimum solubility at 37 °C within the pH range of 1 – 7.5 is 0.191 mg/mL at pH 7.5 (Table 1 and Figure 1). Thus, any administered dose of 47.9 mg or lower will categorize Upadacitinib as highly soluble compound. As per the Reviewer’s assessment, at the proposed dose of 15 mg and the highest dose of 30 mg, the volumes required to dissolve the drug are 78.53 mL and 157.06 mL, respectively, both of which are < 250 mL. Hence, the Applicant’s conclusion that Upadacitinib is considered as a highly soluble compound is found to be acceptable.

Table 1: Solubility of Upadacitinib drug substance at 37 °C in different aqueous media

Medium	Nominal pH	Final pH	Solubility (mg/mL)
0.1 N HCl	1.0	2.57	38.4 ± 1.5
50mM phosphate buffer	2.01	3.08	10.5 ± 0.1
50mM citrate buffer	3.00	3.39	4.48 ± 0.08
50mM citrate buffer	4.01	4.16	1.00 ± 0.01
50mM citrate buffer	5.03	5.01	0.289 ± 0.006
50mM citrate buffer	6.01	5.96	0.196 ± 0.001
50mM phosphate buffer	7.02	7.14	0.194 ± 0.001
50mM phosphate buffer	8.02	7.99	0.200 ± 0.013
50mM carbonate buffer	9.02	9.11	0.199 ± 0.006
Water	6.02	6.92	0.240 ± 0.004
FeSSIF	5.01	5.10	0.455 ± 0.006
FaSSIF	6.50	6.58	0.262 ± 0.003

Figure 1: pH-solubility profile of Upadacitinib drug substance 37 °C



Permeability:

The permeability of Upadacitinib was evaluated using MDCK-WT model at a single concentration of 3 µM with a pan-transporter inhibitor, Cyclosporine A (at 10 µM). The mean P_{app} value of Upadacitinib from two-independent experiments was 8.1×10^{-6} cm/s, which was between the low permeability marker (atenolol) and the high permeability marker (metoprolol) (Table 2). The Applicant has stated that since the P_{app} for Upadacitinib is higher than propranolol (5.9×10^{-6} cm/s), a BCS Class I drug, Upadacitinib is considered as a highly permeable drug per the applicant. However, no formal claim designating Upadacitinib as BCS class 1 drug substance was included in this submission.

Table 2: Cell permeability P_{app} A to B values in MDCK-WT cells

Compound	Concentration	P_{app} (10^{-6} cm/s)		
		Exp 1	Exp 2	Mean
A-1293543	3 µM	9.1	7.0	8.1
Quinidine	1 µM	26	14	20
Atenolol	1 µM	0.34	0.70	0.52
Propranolol	1 µM	5.5	6.2	5.9
Verapamil	1 µM	7.1	12	10
Cimetidine	1 µM	0.87	1.4	1.1
Metoprolol	1 µM	48	34	41

BCS Designation:

Reviewer’s Assessment:

The minimum solubility of Upadacitinib within the pH range of 1 – 7.5 is 0.191 mg/mL at pH 7.5. Hence, at the proposed dose of 15 mg, the volume required for dissolution is 78.53 mL, which is < 250 mL. Hence, Upadacitinib is considered as a highly soluble compound. The mean P_{app} value of Upadacitinib was 8.1×10^{-6} cm/s, which was higher than propranolol (5.9×10^{-6} cm/s), a BCS Class I drug. Hence, Upadacitinib may considered as a highly permeable drug. Based on the high solubility/high permeability, the Applicant has classified Upadacitinib drug substance as a BCS

Class I compound; however, a formal BCS designation claim has not been failed and consequently, currently not accepted as such by the Agency.

Dissolution Method and Acceptance Criteria

1. Dissolution Method:

Selection of Dissolution Apparatus, and rotation speed and Dissolution medium:

Initial dissolution method development utilized USP Apparatus (b) (4) with an agitation speed of (b) (4) rpm and 900 mL of 0.05 M sodium phosphate buffer, pH 6.8. The Applicant stated that this initial method showed discrimination against prototype formulations designed with different in vitro and in vivo performance and was deemed suitable. The release profiles of the 7.5 mg, 15 mg and 30 mg Upadacitinib tablets are shown below in Figure 2.

Figure 2: Dissolution profiles of 7.5 mg, 15 mg and 30 mg Upadacitinib tablets using Apparatus (b) (4) at (b) (4) rpm.



The Applicant stated that during development, tablets were observed (b) (4)
(b) (4)
(b) (4) A comparison of the dissolution profiles of the 30 mg Upadacitinib tablets in 0.05 M sodium phosphate buffer, pH 6.8 is shown below in Figure 3.

Figure 3: Dissolution profiles of 30 mg Upadacitinib tablets in phosphate buffer, pH 6.8 using (b) (4) versus Apparatus 1 at 100 rpm.



The Applicant stated that for the 30 mg tablet, Apparatus 1 at 100 rpm provided a [REDACTED] (b) (4). The Applicant stated that the dissolution profiles for the two strengths are identical using the above dissolution method. The Applicant compared the dissolution profiles of the 30 mg tablet using Apparatus 1 at 100 rpm at various pH [REDACTED] (b) (4) and 50 mM sodium phosphate buffer, pH 6.8 (Figure 4).

Figure 4: Dissolution profiles of the 30 mg Upadacitinib ER tables at various pH



The Applicant stated that the test product shows [REDACTED] (b) (4). To further assess this, the Applicant evaluated the dissolution profiles of the 7.5 mg, 15 mg and the 30 mg strengths at the three different pH conditions (Figures 5A-5C).

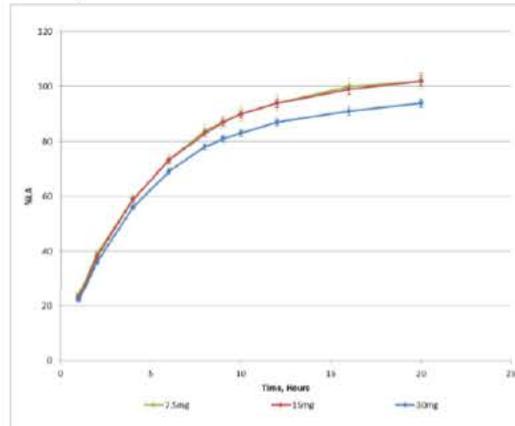
Figure 5A: Dissolution profiles of 7.5 mg, 15 mg and 30 mg Upadacitinib ER tablets in (b) (4) (pH (b) (4))



Figure 5B: Dissolution profiles of 7.5 mg, 15 mg and 30 mg Upadacitinib ER tablets in (b) (4) pH (b) (4)



Figure 5C: Dissolution profiles of 7.5 mg, 15 mg and 30 mg Upadacitinib ER tablets in 50 mM phosphate buffer pH 6.8

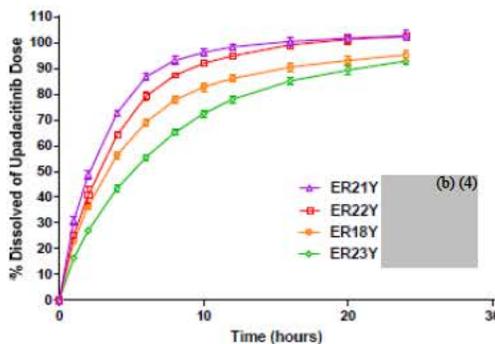


The above data presented in Figures 5A-5C demonstrated that the separation profiles for the three dosage strengths (b) (4). The Applicant stated that due to this reason, (b) (4)

(b) (4) the 50 mM phosphate buffer, pH 6.8 was selected over the other two buffers as the final dissolution medium.

The discriminatory power of the proposed dissolution method was demonstrated via the development of an IVIVC model. Towards the development of an IVIVC model, four formulation variants of the highest strength (30 mg) were manufactured. These products (ER21Y, ER22Y and ER23Y) differed from the prototype test product (ER18Y) (b) (4)

Figure 6: Mean in vitro dissolution profiles for the four ER formulations of Upadacitinib (b) (4) in the proposed dissolution media



As seen in Figure 6, in the proposed dissolution media, the four ER formulations showed different dissolution profiles (b) (4)

(b) (4)

Based on the above data, the dissolution method being proposed by the Applicant is:

Apparatus: USP apparatus 1 (Baskets)
 Medium: 50 mM Phosphate buffer pH 6.8
 Volume: 900 mL
 Temperature: 37 °C
 Speed: 100 rpm
 Time points: 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 Hours

Reviewer's Assessment:

The Reviewer finds the Applicant's justification to use Apparatus 1 as the apparatus of choice for further development to be acceptable. (b) (4)

(b) (4) selection of 50 mM phosphate buffer pH 6.8 as the buffer for dissolution is found acceptable. The Reviewer also assessed the discriminatory ability of the proposed dissolution method. The Reviewer compared the dissolution profiles of the prototype test product containing (b) (4)

The f_2 comparisons between the prototype/target formulation ((b) (4)%) and the altered formulations is shown in the table below:

(b) (4) concentration of the 30 mg strength	f_2 (Reviewer calculated)
(b) (4) % (ER18Y; Target)	-
(b) (4) (ER21Y)	42.74
(ER22Y)	55.07
(ER23Y)	47.92

The f_2 values indicated that the dissolution method could not discriminate between small (b) (4) changes (b) (4). However, the proposed method was able to discriminate between larger (b) (4) changes (b) (4). In addition, there is a rank-order correlation between the in vitro dissolution profiles and the in vivo absorption profiles (see the IVIVC Report in IND 114717). Thus, the Reviewer concludes that the proposed dissolution method is discriminatory.

2. Acceptance criteria:

The Applicant stated that the batch# 17-000591 corresponds to the Proposed Commercial formulation of the extended-release of ER17 tablet. Furthermore, batch# 1000186479 (15 mg SQB) was used in the pivotal bioequivalence study. The data (in vitro dissolution and PK) from this batch was used towards the construction and validation of the IVIVC model for the 15 mg strength. The individual 12-unit in vitro dissolution data has been presented in Appendix 1: Tables 1A and 1B. Based on the data, the Applicant proposed the following acceptance criteria:

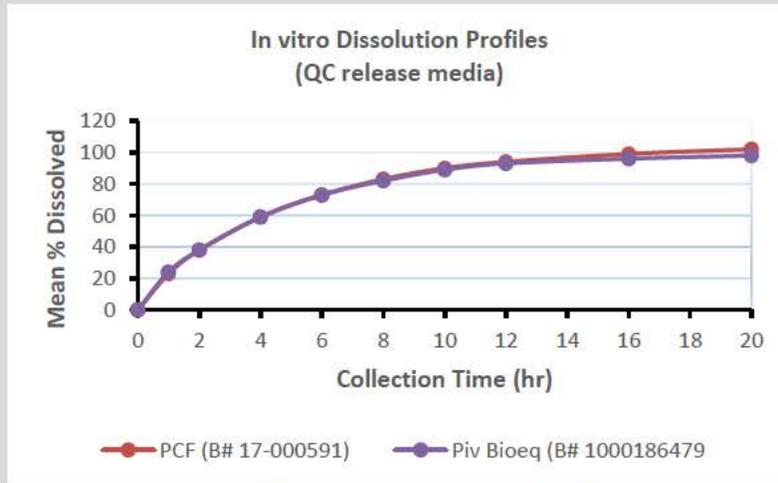
1 hour: (b) (4) %
 4 hours: (b) (4) %

12 hours: NLT (b)(4)0%

Reviewer's Assessment:

The dissolution profiles for the ER17 batch# 17-000591 and batch 1000186479 are shown below in Figure 7:

Figure 7: In vitro dissolution profiles for the 15 mg Proposed Commercial Formulation (ER17; batch# 17-000591) and batch# 1000186479 that was used in the Pivotal Bioequivalence study in QC release media



Based on the data provided in Appendix 1: Tables 1A and 1B, the mean % dissolved at the 1-hour time point is 24% with a range of 22% – 24%. The Applicant has proposed an acceptance criterion of (b)(4)% for the 1-hour time point. The acceptance criterion for the 1-hour time point is (b)(4) (b)(4). The mean % dissolved at the 4-hour time point is 59% with a range of 56% – 60%. The Applicant has proposed an acceptance criterion of (b)(4)% for the 4-hour time point. The acceptance criterion for the 4-hour time point is (b)(4). Based on the IVIVC model, (b)(4) (b)(4)

(b)(4) and is not anticipated to have any efficacy concerns as per Clinical Team's input. Hence, the proposed specifications for the 1-hour and 4-hour time points are found to be acceptable. (b)(4) (b)(4)

(b)(4) Hence, the Applicant's proposed acceptance criterion of NLT (b)(4)% at the 12-hour time point is found to be acceptable. The Biopharmaceutics Reviewer finds the proposed acceptance criteria below to be acceptable:

- 1 hour: (b)(4)%
- 4 hours: (b)(4)%
- 12 hours: NLT (b)(4)%

Application of dissolution/IVIVC:

The Applicant stated that since the three strengths (7.5 mg, 15 mg and 30 mg) are proportionally similar, the highest strength (30 mg) was selected to be evaluated in an IVIVC. The composition of the 7.5 mg, 15 mg and 30 mg tablets used in Phase 3 studies is shown in Table 3A and that of the 15 mg and 30 mg Upadacitinib ER Commercial Formulations is shown in Table 3B.

Table 3A: Composition of 7.5 mg, 15 mg and 30 mg Phase 3 Upadacitinib ER formulations

Component	Function	Quality Standard	ER ⁶ 7.5 mg (Japan Only)		ER ⁷ 15 mg		ER ⁸ 30 mg	
			Amount (mg)/Tablet	% in Tablet	Amount (mg)/Tablet	% in Tablet	Amount (mg)/Tablet	% in Tablet
Upadacitinib (b) (4)	Active							
Microcrystalline Cellulose							(9) (9)	
Mannitol								
Tartaric Acid								
Hydroxypropyl Cellulose (b) (4)								
Colloidal Silicon Dioxide								
Magnesium Stearate								(b) (4)

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Table 3B: Composition of the 15 mg and 30 mg Commercial Formulation Upadacitinib ER tablets

Component	Quality Standard	Function	15 mg ER17		30 mg ER18	
			Amount (mg)/Tablet	% in Tablet	Amount (mg)/Tablet	% in Tablet
						(b) (4)

Reviewer's Assessment:

According to the March 2014 "Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations", the guidance defines proportionally similar for high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low in the following way: (1) the total weight of the dosage form remains nearly the same for all strengths (within ± 10 % of the total weight of the strength on which a BE was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. For the 30 mg and the 15 mg strengths, the weights of the active ingredient are (b) (4) %

and (b) (4) % that of the total weight (b) (4). The 15 mg strength can be considered as a high potency drug based on the weight of the active ingredient being (b) (4) % (b) (4) %. The 30 mg strength can be considered as a weakly high potency drug based on the weight of the active ingredient being in the range of (b) (4) % (b) (4) % of the total weight (b) (4). Since the weight of the active ingredient is within 10% of the total weight of the strength of which the BE has been performed 30 mg, the 15 mg and the 30 mg strengths are considered proportionally similar in their composition. Furthermore, in the Scientific Advice that was provided by the Agency via a Meeting Correspondence, the Agency agreed that the 15 mg and the 30 mg strengths of the Upadacitinib ER tablets used in the Phase 3 studies were considered proportionally similar in their composition.

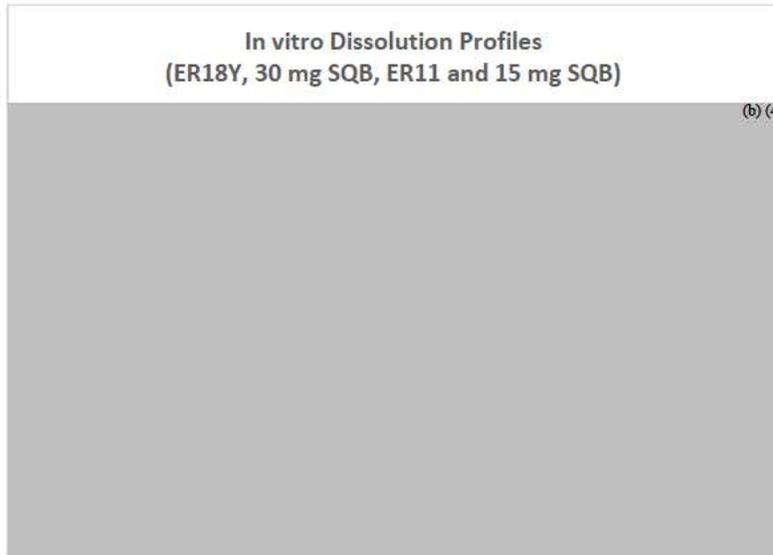
Four Upadacitinib ER formulations including the proposed commercial formulation were designed and tested with an aim to investigate the relationship between in vitro dissolution rate and the corresponding in vivo performance (M15-868 study). These formulations were designed to have similar release mechanism to the proposed commercial formulation (b) (4). All the four formulations had similar compositions (b) (4).

A level A IVIVC was developed using the PK data from study M15-868 conducted under fasting conditions from four ER formulations of Upadacitinib ER tablets (Report R&D/17/1129). The details of the IVIVC that was developed for the 30 mg strength and the Reviewer's evaluation of the IVIVC model for the 30 mg strength have been included in the IND 114717 report.

External Predictability and Applicability of the IVIVC to other strengths:

The Applicant submitted additional data to predict the PK profiles of two formulations used in other studies – ER11 and 30 mg SQB (Site Qualification Batch). These two formulations are of the 30 mg strength. The 30 mg SQB formulation was evaluated in the pivotal BE study (report M15-878) and the ER11 formulation was evaluated in the bioavailability study (report M14-769). The in vitro dissolution profiles for 30 mg SQB and ER11 are shown in Figure 8. The Applicant has stated that the dissolution profiles of 30 mg SQB and the ER11 formulations are similar to the ER18Y target based on their f_2 values being >50 when compared to the ER18Y formulation.

Figure 8: In vitro dissolution profiles of ER18Y and formulations used in other studies – ER11, SQB-30 mg and SQB-15 mg



The PK parameters of the two 30 mg formulations – ER11 and 30 mg SQB was predicted by the Applicant using the IVIVC model, and the results are summarized in Table 5.

Table 5: IVIVC model predictability for the 30 mg ER11, SQB-30 mg and SQB-15 mg formulations

Formulation	Study (source of observed data)	Parameter	Predicted Geometric Mean	Observed Geometric Mean	%Difference
15 mg - SQB	M15-878	AUC _{INF_obs}			(b) (4)
15 mg - SQB	M15-878	C _{max}			
30 mg - SQB	M15-878	AUC _{INF_obs}			
30 mg - SQB	M15-878	C _{max}			
30 mg - ER11	M14-679	AUC _{INF_obs}			
30 mg - ER11	M14-679	C _{max}			

Reviewer’s Assessment:

The Reviewer notes that the predicted PK parameters (AUC and C_{max}) for each of the two 30 mg ER formulations (ER11 and 30 mg SQB) match the observed PK parameters. The %PE for AUC and C_{max} for each of these formulations is <15%. However, since the Applicant is not requesting approval of the 30 mg strength, the Reviewer concludes that constructing the model using only the 30 mg strength and evaluating its applicability to the 30 mg ER11 and 30 mg SQB formulations is not relevant.

In the NDA submission, the Applicant is requesting approval of the 15 mg strength of the product and not of the 30 mg strength. Since the 15 mg and the 30 mg tablet formulations are proportionally similar (b) (4) the Applicant submitted the in vitro dissolution data on the 15 mg strength of the product (15 mg SQB). The Applicant stated that the dissolution profile of 15 mg SQB is similar to the ER18Y target based on its f₂ values in being >50 when compared to the ER18Y formulation (Figure 7). The PK parameters of the 15 mg formulations – 15 mg SQB was predicted by the Applicant using the IVIVC model, and the results are summarized in Table 5.

Reviewer's Assessment:

The Reviewer notes that the predicted C_{max} for the 15 mg formulation (% Difference = ^{(b) (4)}) does not meet the acceptance criterion (the %PE for AUC and C_{max} for each of formulation should be <15%). Hence, the Reviewer concludes that the IVIVC model that has been constructed using the 30 mg formulations may not be robust enough to accurately predict the 15 mg formulation.

Furthermore, the Reviewer notes that since the Applicant is requesting approval of the 15 mg strength of the product (and not the 30 mg strength), merely predicting the PK parameters for the 15 mg strength using the IVIVC model that was constructed solely with several release profiles of the 30 mg strength is not appropriate. The Reviewer emphasized during the review cycle that the IVIVC model should be reconstructed and revalidated by incorporating the in vivo PK data and the in vitro dissolution data of the 15 mg SQB formulation.

The Reviewer reconstructed the IVIVC model (with the same parameters as that were used to construct the original IVIVC model) with the in vivo PK and in vitro dissolution data for the 15 mg data that was submitted by the Applicant. The predictability of the IVIVC model was evaluated using the 15 mg SQB; ER21Y; ER18Y; and ER23Y and the internal validation formulations and ER22Y as the external validation formulation (Table 6).

Table 6: Predictability of IVIVC using 15 mg SQB; ER21Y; ER18Y; and ER23Y as the internal validation formulations and ER22Y as the external validation formulation

Formulation	Parameter	Reviewer's Evaluation		
		Predicted	Observed	%PE
15mg SQB int	AUC _{inf}	248.9	228.8	8.8
15mg SQB int	C _{max}	25.1	24.1	4.3
ER18Y int	AUC _{inf}	462.5	485.9	-4.8
ER18Y int	C _{max}	47.2	51.4	-8.2
ER21Y int	AUC _{inf}	573.3	547.9	4.6
ER21Y int	C _{max}	63.8	70.4	-9.4
ER22Y ext	AUC _{inf}	531.7	510.9	4.1
ER22Y ext	C _{max}	55.1	63.4	-13.2
ER23Y int	AUC _{inf}	388.4	428.6	-9.3
ER23Y int	C _{max}	35.8	40.6	-11.9
Ave int	AUC _{inf}	400.2	401.9	6.9
Ave int	C _{max}	40.6	45.4	8.4

Based on the prediction data shown in Table 6, the PK parameters (C_{max} and AUC) for each of the four ER formulations used in generating the IVIVC model (15 mg SQB, ER18Y, ER21Y and ER23Y) match the observed PK parameters. The %PE for C_{max} and AUC for each of these four internal validation formulations is <15% with the Average %PE <10%. The IVIVC model was able to predict the fifth ER formulation (ER22Y), which was used for the external validation.

Cross-validation of the reconstructed IVIVC using the leave-one-out cross validation approach:

The Reviewer also performed cross-validation of the IVIVC model (constructed with the 15 mg SQB) using the leave-one-out approach. Herein, the IVIVC model was evaluated using each of the four 30 mg ER formulations as an external validation and the remaining four formulations as the model-building and internal validation. The results of the cross-validation are shown in Table 6

above (ER22Y as external) and Tables 7A-7C (ER21Y, ER23Y and ER18Y as external). The 15 mg SQB formulation was maintained as the internal validation formulation in each of the cases.

Table 7A: Cross-validation results for the non-linear 15 mg SQB IVIVC model using the leave-one-out approach (ER21Y as the external validation)

Formulation	Parameter	Reviewer's Evaluation		
		Predicted	Observed	%PE
15mg SQB int	AUC _{inf}	249.6	228.8	9.1
15mg SQB int	C _{max}	25.6	24.1	6.4
ER18Y int	AUC _{inf}	463.7	485.9	-4.6
ER18Y int	C _{max}	48.3	51.4	-6.0
ER21Y ext	AUC _{inf}	574.4	547.9	4.8
ER21Y ext	C _{max}	65.2	70.4	-7.4
ER22Y int	AUC _{inf}	532.9	510.9	4.3
ER22Y int	C _{max}	56.2	63.4	-11.4
ER23Y int	AUC _{inf}	389.6	428.6	-9.1
ER23Y int	C _{max}	36.6	40.6	-9.9
Ave int	AUC _{inf}	393.7	401.9	6.7
Ave int	C _{max}	39.9	45.4	8.5

Table 7B: Cross-validation results for the non-linear 15 mg SQB IVIVC model using the leave-one-out approach (ER23Y as the external validation)

Formulation	Parameter	Reviewer's Evaluation		
		Predicted	Observed	%PE
15mg SQB int	AUC _{inf}	242.3	228.8	5.9
15mg SQB int	C _{max}	25.8	24.1	7.2
ER18Y int	AUC _{inf}	449.7	485.9	-7.4
ER18Y int	C _{max}	49.8	51.4	-3.1
ER21Y int	AUC _{inf}	564.6	547.9	3.0
ER21Y int	C _{max}	66.9	70.4	-4.9
ER22Y int	AUC _{inf}	519.4	510.9	1.7
ER22Y int	C _{max}	56.6	63.4	-10.7
ER23Y ext	AUC _{inf}	373.6	428.6	-12.8
ER23Y ext	C _{max}	36.9	40.6	-9.1
Ave int	AUC _{inf}	422.8	420.0	4.5
Ave int	C _{max}	47.0	48.5	6.5

Table 7C: Cross-validation results for the non-linear 15 mg SQB IVIVC model using the leave-one-out approach (ER18Y as the external validation)

Formulation	Parameter	Reviewer's Evaluation		
		Predicted	Observed	%PE
15mg SQB int	AUC _{inf}	243.5	228.8	6.4
15mg SQB int	C _{max}	25.7	24.1	6.6
ER18Y ext	AUC _{inf}	451.9	485.9	-7.0
ER18Y ext	C _{max}	49.3	51.4	-4.2
ER21Y int	AUC _{inf}	565.8	547.9	3.3

ER21Y int	C _{max}	66.2	70.4	-6.0
ER22Y int	AUC _{inf}	521.5	510.9	2.1
ER22Y int	C _{max}	56.3	63.4	-11.3
ER23Y int	AUC _{inf}	376.4	428.6	-12.2
ER23Y int	C _{max}	36.7	40.6	-9.7
Ave int	AUC _{inf}	405.5	407.0	5.9
Ave int	C _{max}	43.3	45.7	8.4

The Reviewer notes that with the 15 mg SQB IVIVC model, for each of the combinations wherein a different formulation is set as the external validation formulation, the predicted PK parameters (AUC and C_{max}) for each of the ER formulations match the observed PK parameters. The %PE for AUC and C_{max} for each of the formulations is <15%. The Reviewer finds the leave-one-out approach for predicting the PK parameters for the 15 mg SQB and the four formulations of the 30 mg strength by the Reviewer reconstructed IVIVC model as acceptable.

Evaluating the acceptable variation and establishing a “safe space”:

To assess the acceptable variation and establish a safe space where the 15 mg SQB IVIVC model predicts are BE (the difference between the upper and lower bound in predicted AUC and C_{max} are less than (b) (4) %), the Reviewer predicted the PK parameters for four hypothetical variants of 15 mg SQB target wherein the dissolution profiles of the 15 mg SQB target were altered by either (b) (4) % (Table 8).

Table 8: Reviewer’s evaluation of the IVIVC model for establishing a safe space around the target 15 mg SQB formulation.

Formulation	Parameter	Reviewer’s Evaluation			
		Predicted	Target (15mg SQB)	% Difference in predicted C _{max} and AUC (relative to target)	% Difference in predicted C _{max} and AUC (relative to Upper and Lower limits)
15mg SQB (b) (4) %	AUC _{inf}				(b) (4)
15mg SQB %	C _{max}				
15mg SQB %	AUC _{inf}				
15mg SQB %	C _{max}				
15mg SQB %	AUC _{inf}				
15mg SQB %	C _{max}				
15mg SQB %	AUC _{inf}				
15mg SQB %	C _{max}				
15mg SQB %	AUC _{inf}				
15mg SQB %	C _{max}				
15mg SQB (b) (4) %	AUC _{inf}				
15mg SQB %	C _{max}				
15mg SQB %	AUC _{inf}				
15mg SQB %	C _{max}				

Based on the Reviewer’s assessment, the IVIVC model has the ability to predict the BE with an acceptable variation and establish a safe space lower than (b) (4) % change in the target formulation’s in vitro dissolution (wherein the % difference in AUC is (b) (4) %). Hence, this model is not applicable for establishing wider dissolution acceptance criteria than (b) (4)

Clinical relevance of Proposed dissolution acceptance criteria and IVIVC predictions:

Based on the original 30 mg IVIVC model, the Applicant predicted exposures (AUC and C_{max}) through convolution of the dissolution profiles (b) (4) of the ER18Y target formulation. The % differences in the predicted exposure were generated for AUC and C_{max} by comparing predicted exposures from the dissolution specification relative to the observed target formulation (Table 9).

Table 9: Predicted exposures for Upper and Lower Dissolution specifications relative to the ER18Y target formulation using the Applicant’s original 30 mg IVIVC model

Dissolution Specification	Parameter	Predicted	Observed	% Difference
(b) (4)				

Based on the 30 mg IVIVC model, the Upadacitinib ER formulations that were at the upper and lower boundaries of the (b) (4)% specifications were predicted to have a C_{max} difference of (b) (4)% and (b) (4)% and an AUC difference of (b) (4)% and (b) (4)%. The clinical relevance of the proposed dissolution specifications was evaluated in the exposure-response analyses for efficacy and safety in subjects with RA. The Applicant stated that they performed simulations to predict the impact of (b) (4)% increase (higher (b) (4)%) in exposure (of the 15 mg target) on the safety profile. In addition, they also performed simulations to predict the impact of (b) (4)% decrease (lower (b) (4)%) in exposure (of the 15 mg target) on the efficacy profile

Reviewer’s Assessment:

The Reviewer notes that the predicted exposures for the Upper and Lower limits of dissolution specifications have been evaluated relative to the ER18Y target formulation using the original 30 mg IVIVC model. Hence, the values of (b) (4)% and (b) (4)% for the C_{max} difference and (b) (4)% and (b) (4)% for the AUC difference are not acceptable. The Reviewer recommends that the Upper and Lower limits of dissolution specifications be evaluated relative to the 15 mg SQB as the target formulation using the 15 mg IVIVC model. The Reviewer predicted the exposures for the Upper and Lower limits of dissolution specifications relative to the 15 mg SQB as the target formulation using the 15 mg IVIVC model (Table 10).

Table 10: Predicted exposures for Upper and Lower Dissolution specifications relative to the 15 mg SQB target formulation using the Reviewer’s reconstructed 15 mg IVIVC model

Formulation	Parameter	Reviewer’s Evaluation		
		Predicted	Observed for 15 mg SQB	% Difference in predicted C _{max} and AUC (relative to target)
15mg SQB (b) (4) %	AUC _{inf}	(b) (4)		
15mg SQB %	C _{max}			
15mg SQB %	AUC _{inf}			
15mg SQB %	C _{max}			

Based on this 15 mg IVIVC model, the Upadacitinib ER formulations that were at the upper and lower boundaries of the (b) (4) specifications were predicted to have a C_{max} difference of (b) (4) (b) (4)% and an AUC difference of (b) (4) (b) (4)%. The Biopharmaceutics Reviewer consulted the Clinical Reviewer for establishing the acceptable boundaries for efficacy and safety. According to the Clinical Reviewer, a (b) (4) in PK parameters relative to the 15 mg strength would correspond to a (b) (4) tablet. The Clinical Reviewer does not anticipate any safety concerns associated with this strength. Similarly, a (b) (4) (b) (4)% in PK parameters relative to the 15 mg strength would correspond to a (b) (4) tablet. The Clinical Reviewer does not anticipate any efficacy concerns associated with this strength. The Biopharmaceutics Reviewer finds this acceptable.

Reviewer’s Overall Assessment of the IVIVC Model:

A non-linear level A IVIVC model developed by the Applicant using the four 30 mg and one 15 mg ER formulations meets the internal and external predictability. Since the IVIVC model was constructed using both the 30 mg and 15 mg strengths, the model is applicable to both the strengths. Based on the Reviewer’s analysis, the IVIVC model is able to predict the BE with an acceptable variation of lower than (b) (4)% change in the target formulation’s in vitro dissolution. However, based on exposure-response analysis, a safe space of mean (b) (4)% was been acceptable. It should be noted that, during the review cycle, the Applicant was advised to rely on other modeling approaches (e.g. mechanistic) with the possibility of expanding the safe space.

In vitro alcohol dose dumping studies:

The Applicant stated that the in vitro alcohol dose dumping studies were performed on the 30 mg strength and not on the 15 mg strength. The dose dumping studies were performed under two pH conditions – 0.1 N HCl (simulating the gastric environment) and at pH 6.8 (simulating the intestinal environment). Alcohol at four levels (0%, 10%, 20%, and 40%) was added to either 0.1N HCl or pH 6.8 media. The Applicant stated that the testing conditions (12-tablets; time points), including apparatus type, medium and other parameters were in accordance with the proposed dissolution method. The dissolution profiles in 0.1N HCl and phosphate buffer, pH 6.8 are depicted in Figure 9A and Figure 9B, respectively.

Figure 9A: In vitro dissolution profiles of the 30 mg ER formulation in 0.1N HCl with various concentrations of alcohol

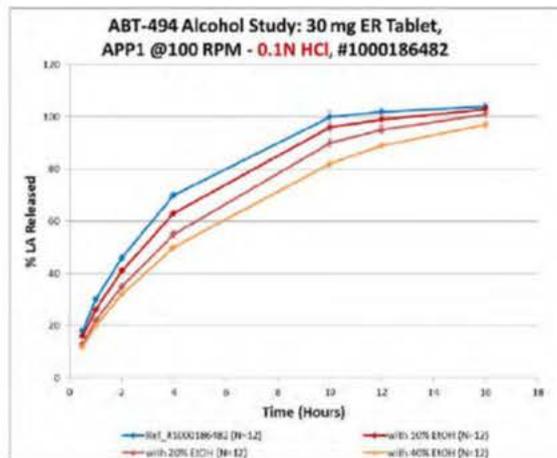
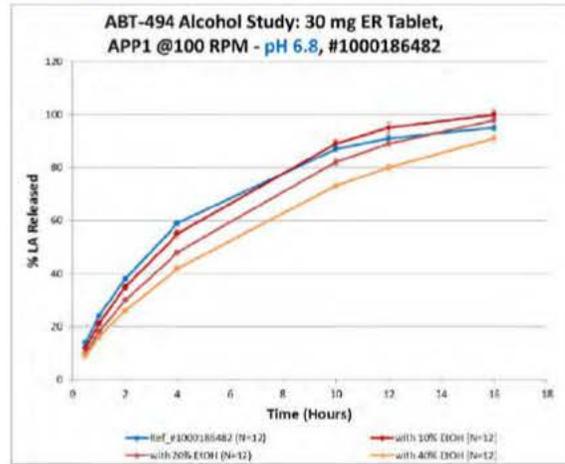


Figure 9B: In vitro dissolution profiles of the 30 mg ER formulation in phosphate buffer, pH 6.8 with various concentrations of alcohol



The dissolution profiles demonstrate that in both the media (0.1N HCl and phosphate buffer, pH 6.8), the drug release was slowed down by the presence of alcohol in the solution. A consistent trend was observed where higher alcohol levels resulted in slower release profiles. The data suggests that there is no dose dumping due to the presence of alcohol. The Applicant provided the f_2 values comparing the dissolution profiles in media alone compared to the dissolution profiles in media + alcohol (Table 11).

Table 11: f_2 comparisons for dissolution profiles in alcohol dose dumping studies

Condition, pH	0% EtOH	10% EtOH	20% EtOH	40% EtOH
0.1N HCl	Ref	66	49.2	42.2
pH 6.8	Ref	75.7	58.6	47.7

The dissolution profiles in media alone compared to the dissolution profiles in media + 10% alcohol and in media + 20% alcohol yielded f_2 values ≥ 50 media alone indicating that the dissolution profiles in the presence of up to 20% alcohol were similar to those in the absence of alcohol. The dissolution profiles in media + 40% alcohol yielded f_2 values < 50 when compared to media alone. This indicated that a decrease in the release in 40% alcohol-media was significant compared to the release in media alone. The Applicant stated that since the sustained gastric or intestinal alcohol levels of 20% or higher were not expected to be achieved in patients, the reduction in the release rate at very high alcohol levels was not clinically relevant.

Reviewer’s Assessment:

Since the 15 mg and 30 mg tablet formulations are proportionally similar, the Reviewer considers performing the dose dumping studies on the 30 mg strength to be acceptable. The Reviewer considers the alcohol concentrations (0% – 40%) and the testing conditions (12-tablets; time points, including apparatus type, medium and other parameters) used for the in vitro alcohol dose dumping studies to be acceptable. Based on the 12-unit dissolution data that was submitted by the Applicant, the Reviewer calculated f_2 values were found to be in accordance with the Applicant’s f_2 values. The Reviewer concludes that there is no increase in dissolution or “dose-dumping” in the presence of alcohol in the media. Although there appears to be a reduction in the release

profile in the presence of alcohol, the release profiles in 40% alcohol-media were significantly different compared to that in media alone. The Applicant's justification that since the sustained gastric or intestinal alcohol levels of 20% or higher were not expected to be achieved in patients, the reduction in the release rate at very high alcohol levels was not clinically relevant is found to be acceptable. The Reviewer notes that the alcohol dose-dumping studies have not been performed at pH (b) (4). However, based on lack of alcohol dose-dumping in (b) (4) and at pH 6.8, the Reviewer does not anticipate a dose-dumping effect at pH (b) (4). Overall, the Reviewer concludes that there is no significant effect of alcohol on the release profile of the product. The Reviewer finds the results from the alcohol dose dumping studies to be acceptable.

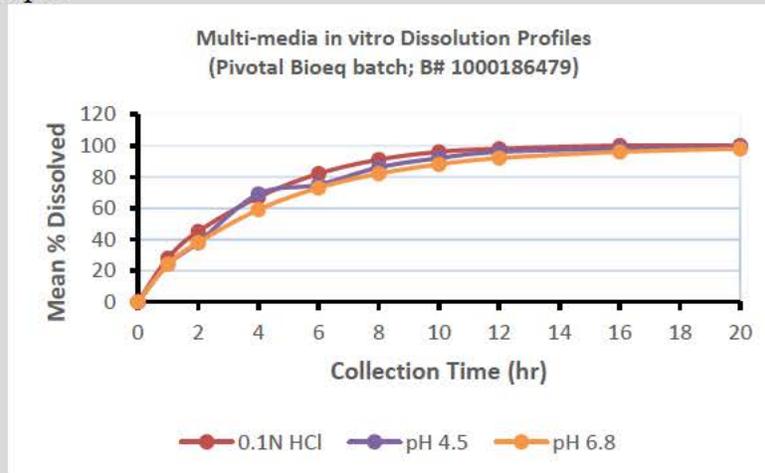
Multi-media dissolution profiles:

The Applicant performed in vitro dissolution studies on the 15 mg Pivotal Bioequivalence batch (batch# 1000186479) and the Proposed Commercial Formulation (ER17; batch# 17-000591) in media of three different pH – 0.1N HCl (pH 1.2; simulating the gastric pH), pH 4.5 (simulating the upper intestinal pH) and pH 6.8 (simulating the lower intestinal pH). The Applicant stated that the release profiles of the 15 mg drug product were similar in all the three media and no dose dumping was observed in any media.

Reviewer's Assessment:

The Reviewer plotted the dissolution profiles for the Pivotal Bioequivalence batch (batch# 1000186479) and the Proposed Commercial Formulation (ER17; batch# 17-000591) in the three media in Figure 10A and Figure 10B, respectively.

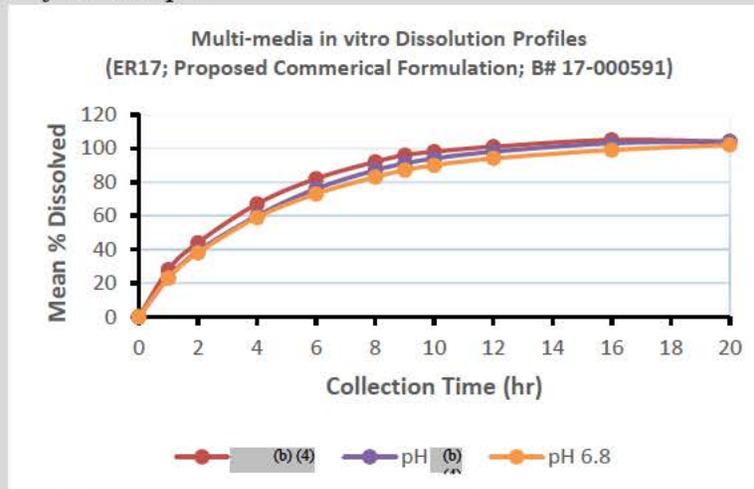
Figure 10A: In vitro dissolution profiles of the Pivotal Bioequivalence batch (batch# 1000186479) in media of various pH



The Reviewer observed that the release profiles of the 15 mg drug product were similar in all the three media. The Reviewer compared the dissolution profiles for the three by calculating the f_2 values between the profile in pH 6.8 (finalized dissolution media) to the profiles in pH 1.2 and pH 4.5 (see below)

Dissolution medium	f_2 (Reviewer calculated)
pH 6.8	-
0.1N HCl (pH 1.2)	55.5
pH 4.5	65.6

Figure 10B: In vitro dissolution profiles of the Proposed Commercial Formulation ER17 batch# 17-000591 in media of various pH



The Reviewer observed that the release profiles of the 15 mg drug product were similar in all the three media. The Reviewer compared the dissolution profiles for the three by calculating the f_2 values between the profile in pH 6.8 (finalized dissolution media) to the profiles in pH (b)(4) and pH (b)(4) (see below)

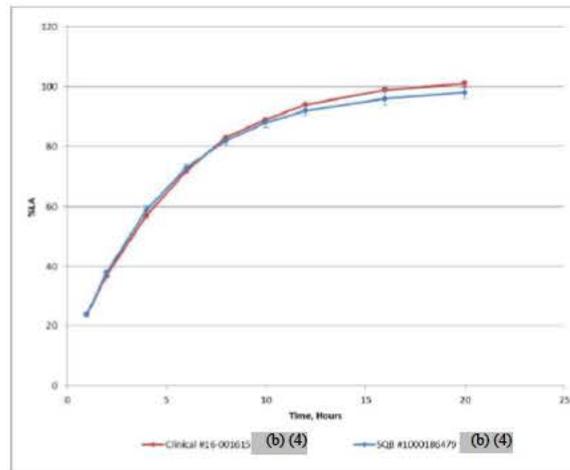
Dissolution medium	f_2 (Reviewer calculated)
pH 6.8	-
(b)(4)	55.1
pH (b)(4)	75.6

Based on the f_2 values, the Reviewer concludes that the dissolution profiles for the 15 mg strengths are similar in the three media, and there is no dose-dumping at any pH. The Reviewer finds the results from the multi-media dissolution studies to be acceptable.

Bridging of formulations:

The modifications in the formulation of the tablets evaluated in the Phase 3 trials to the Proposed Commercial Formulation include (b)(4). In addition, the manufacturing process used for the Phase 3 supplies differed from the Proposed Commercial process. The Phase 3 supplies were manufactured (b)(4) (b)(4) whereas the Proposed Commercial Process is (b)(4) (b)(4). Furthermore, the manufacturing site for the Phase 3 tablets (Abbvie Waukegan Rd, North Chicago, IL) is different from the Commercial manufacturing site (Abbvie, Sligo, Ireland). The Applicant has stated that linkage of Phase 3 formulations to the Commercial formulation has been demonstrated by in vitro and in vivo comparisons. For in vitro comparison, the dissolution profile of the (b)(4) formulation (Commercial formulation) for the 15 mg strength was compared to the dissolution profile of the (b)(4) formulation using the finalized dissolution method (Figure 11).

Figure 11: In vitro dissolution profiles for the 15 mg (b)(4) formulation (Proposed Commercial Formulation) and the 15 mg (b)(4) formulation (Phase 3 formulation) using the finalized dissolution method



The Applicant has stated that the dissolution profiles between the two formulations were similar and the f_2 values between the two profiles was ≥ 76.3 (The Applicant performed the bridging studies on the 7.5 mg, 15 mg and the 30 mg strengths. The Applicant stated that the f_2 values for the three strengths range from 76.3 to 90.8).

Reviewer's Assessment:

Based on the submitted information, the dissolution profile of the Phase 3 formulation (b) (4) (b) (4) batch appears to be similar to that Commercial Formulation (b) (4) (b) (4) batch ($f_2 > 50$). However, the Applicant did not provide the 12-unit dissolution data for the (b) (4) batch to calculate and confirm the f_2 value that was reported by the Applicant. This is not of concern as the dissolution profiles for the two formulations appear to be similar up to a release of 80 - 85%. The Reviewer notes that in addition to the *in vitro* comparison, the Applicant has performed a bioavailability study under fasting conditions according to a randomized, 2-period crossover design in 40 healthy subjects comparing the Phase 3 formulation to the Commercial formulation. The Clinical Pharmacology Reviewer stated that under fasting conditions the 15 mg Commercial Formulation (ER17) was bioequivalent to the Phase 3 (ER7) formulation. From the Biopharmaceutics perspective, the Reviewer concludes that the bridging of the two formulations has been adequately established, and that the two formulations are similar to each other.

Stability of exhibit batches:

Reviewer's Assessment:

The stability studies have been performed under three conditions – accelerated (40 °C/75% RH), intermediate (30 °C/75% RH) and long-term conditions (25 °C/60% RH). The dissolution data for the stability studies at the 9-month and 12-month time points do not suggest any loss of stability. The stability data will be further reviewed by the DS or DP reviewer.

Extended Release Claim:

The Applicant's data for the extended-release designation claim is derived from the results of study M14-680. This study evaluated the bioavailability of Upadacitinib ER formulation (Phase 3 formulation) to the Upadacitinib IR capsule formulation (Phase 2 formulation) under fasting conditions, and the effect of food on the 30 mg strength of the Upadacitinib ER formulation in healthy subjects.

The ER formulation (15 mg QD) was developed to decrease the peak-to-trough fluctuations in plasma concentrations with the once-daily dosing and achieving daily AUC₀₋₂₄ and minimum concentration (C_{min}) comparable to the IR dose of 6 mg twice daily. The mean fluctuation index in plasma concentrations at steady state over a 24-hour period was 2.5 for the 15 mg QD-ER formulation and 2.6 for the 6 mg BID-IR formulation. Multiple dosing of the 15 mg QD regimen of Upadacitinib ER formulation provided equal AUC to 6 mg BID of Upadacitinib IR capsule formulation under fasting conditions (Table 12).

Table 12: Comparison of PK parameters for multiple doses of 15 mg QD ER7 formulations and the 6 mg BID of the Immediate Release capsule formulations under fasting conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen L vs. Regimen K	C _{max}	30.34	33.40	0.909	0.736 – 1.122
	AUC ₀₋₂₄	270.63	288.29	0.939	0.837 – 1.053
	C ₂₄	2.90	3.51	0.826	0.646 – 1.057
	C _{min}	2.86	2.62	1.090	0.852 – 1.395

Regimen K = 6 mg BID of upadacitinib (2 × 3 mg immediate-release capsules) × 7 days under fasting conditions (Reference for L).

Regimen L = 15 mg QD of upadacitinib once-daily tablet formulation (ER7) × 7 days under fasting conditions (Test for K).

The Upadacitinib ER formulation provided a similar fluctuation index over a 24-hour period with once-daily dosing as opposed to needing twice-daily dosing of the IR formulation. The criteria for no dose dumping in the ER claim was supported by the food effect evaluation, which revealed a 20% - 35% increase in C_{max} and AUC upon co-administration with a high-fat/high-calorie meal (Table 13).

Table 13: PK parameters of Upadacitinib ER formulations (15 mg and 30 mg) under fasting and non-fasting conditions

Pharmacokinetic Parameter (units)	Extended Release Regimen			
	Overall Mean (% CV) ^a			
	15 mg Fasting (N = 138)	15 mg Non-Fasting (N = 11)	30 mg Fasting (N = 151)	30 mg Non-Fasting (N = 136) ^b
C _{max} (ng/mL)	27.5 (35, 32 - 38)	36.0 (24)	58.6 (29, 25 - 33)	78.8 (33, 21 - 40)
AUC (ng•h/mL)	246 (26, 25 - 31)	317 (21)	491 (24, 22 - 27)	605 (26, 20 - 30)
t _{1/2} (h) ^c	8.79 (NC)	9.43 (NC)	10.4 (NC)	10.7 (NC)

Based on the exposure-response analysis, the Applicant stated that the increase in PK parameters in the non-fasting state compared to the fasting state were not considered to be clinically relevant and that the release controlling characteristics were preserved (refer to the Clinical Pharmacology Review for more details on this). Additionally, to assess the risk of dose-dumping for the ER product in vivo due to the presence of alcohol, in vitro alcohol dose dumping studies were conducted. The results indicated that the drug release did not increase with the addition of alcohol.

The Applicant also submitted data to demonstrate that the variability for the ER formulation was low. The variability (mean %CV across studies) of C_{max} and AUC was less than 37% for the 15 mg ER formulation (Table 14).

Table 14: Variability of Single dose Upadacitinib in Phase 1 bioavailability studies

Study	Formulation	Dose (mg)	Food Conditions	N	CV%	
					C _{max}	AUC
M13-401	Capsule	1	Fasting	6	31	19
M13-401	Capsule	3	Fasting	6	28	27
M13-401	Capsule	3	Fed	12	22	14
M13-401	Capsule	6	Fasting	6	26	23
M13-401	Capsule	12	Fasting	6	15	15
M13-401	Capsule	24	Fasting	6	12	13
M13-401	Capsule	36	Fasting	6	16	22
M13-401	Capsule	48	Fasting	6	26	17
M14-680	IR Capsule	12	Fasting	11	16	15
M14-680	ER7 Tablet	15	Fasting	11	37	26
M14-680	IR Capsule	24	Fasting	12	37	25
M14-680	ER8 Tablet	30	Fasting	12	33	27
M14-680	ER8 Tablet	30	Fed	12	39	27
M15-878	Phase 3 ER8 Tablet	30	Fasting	42	26	23
M15-878	Commercial Formulation ER18 Tablet	30	Fasting	42	30	24
M15-878	Commercial Formulation ER18 Tablet	30	Fed	42	22	21
M15-878	Phase 3 ER7 Tablet	15	Fasting	40	35	31
M15-878	Commercial Formulation ER17 Tablet	15	Fasting	40	33	25

Based on this information, the Applicant has stated that the 15 mg Upadacitinib meets the criteria presented in FDA 21CFR 320 for an extended release claim.

Reviewer’s Assessment: *The Applicant submitted the following data to support the ER designation claim per 21 CFT 320.25(f):*

- 1. The dissolution profiles of the drug product in the proposed dissolution method (pH 6.8 phosphate buffer), (b) (4) did not show any evidence of in vitro dose dumping. Furthermore, the alcohol-dose dumping studies indicated there was no increase in dissolution or “dose-dumping” in the presence of alcohol in the media at pH 1.2 (0.1N HCl) and at pH 6.8. The claim for no dose dumping was further demonstrated by a food effect evaluation, which resulted in only a 30% increase plasma exposure (both C_{max} and AUC) in the presence of a high fat diet.*
- 2. Under fasting conditions, after multiple dosing, the AUC for the 15 mg (QD) ER formulation was comparable to the IR dose of 6 mg twice daily (the point estimate for AUC₀₋₂₄ = 0.939 (0.837 – 1.053) indicating that a less frequent dosing interval with the ER formulation is able to achieve a comparable AUC as that of the IR formulation. The mean fluctuation index in plasma concentration at steady state over a 24-hour period between the 15 mg QD-ER formulation was similar to the 6 mg BID-IR formulation (2.5 for the 15 mg QD-ER formulation and 2.6 for the 6 mg BID-IR formulation).*
- 3. The drug product’s formulation provides consistent PK performance between the individual dosage units as evidenced from the variability (mean %CV across studies) of C_{max} and AUC being less than 37% for the 15 mg ER formulation.*

The Reviewer concludes that the information submitted adequately supports the Extended Release claim per 21 CFR 320.25(f).

Biowaiver Request:

Reviewer’s Assessment:

The Applicant has not requested any biowaiver in this submission.

**Appendix 1
Dissolution and Data Tables**

Table 1A: 12-unit in vitro dissolution data for the 15 mg strength batch# 1000186479 corresponding to the Pivotal Bioequivalence study (and used to construct and validate the IVIVC model for the 15 mg strength) of the extended-release tablet in the proposed dissolution conditions

Time (hours)	1	2	4	6	8	10	12	16	20
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	24	38	59	73	82	88	92	96	98
SD	0.6	0.8	1.3	1.2	1.4	1.7	1.7	2.1	1.9
%RSD	2.5	2.2	2.2	1.7	1.7	1.9	1.9	2.2	1.9

Table 1B: 12-unit in vitro dissolution data for the 15 mg strength batch# 17-000591 corresponding to the Proposed Commercial formulation of the extended-release of ER17 tablet in the proposed dissolution conditions

Time (hours)	1	2	4	6	8	9	10	12	16	20
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	23	38	59	73	83	87	90	94	99	102
SD	0.7	1.0	1.0	1.1	1.2	1.3	1.3	1.6	1.8	1.9
%RSD	3.1	2.6	1.7	1.5	1.4	1.4	1.4	1.7	1.8	1.8

Appendix 2:**IR comments and Applicant's Response to IR:**

On 3/19/2019, the following IR comments were sent to the Applicant. On 4/9/2019, the Applicant responded to the IR. The Applicant's response to the IR and the Reviewer's assessment are included below.

IR Item 1:

The 12-unit dissolution data for the 15 mg Tablet, #17-000591 has been presented in module 3.2.P.2.2.3 under "Data tables of Individual Dissolution Results". Please clarify whether Tablet, #17-000591 corresponds to the Proposed Commercial Formulation, Extended-release ER17 tablet. Should tablet, #17-000591 differ from the ER17 tablet, please submit the detailed 12-unit dissolution release profile data for this formulation (individual, mean, range, %CV, and mean profiles) using the proposed dissolution method.

Applicant's Response to IR Item 1:

Tablet batch (b) (4) is representative of the Proposed Commercial Formulation. They are tablets produced (b) (4)

(b) (4)
Additionally, 12-unit dissolution profile data at three pH conditions for the 15 mg commercial-site-stability batch which was used in the pivotal bioequivalence study is provided in the IR response in Tables 12-14.

Reviewer's assessment:

The Reviewer acknowledged the Applicant's response. However, Reviewer needed further clarification whether the Proposed Commercial Formulation batch (b) (4) was identical to batch 17-000591. Hence an email was sent to the Applicant on 4/11/2019, the Applicant was requested to clarify this information. The contents of the email are stated below:

"We acknowledge your IR response that was submitted on April 9, 2019 (eCTD Sequence 0013). As stated on page 30, please clarify whether batch # (b) (4) that is representative of the Proposed Commercial Formulation is identical to batch# 17-000591 – the data for which has been presented in module 3.2.P.2.2.3 under "Dissolution tables of Individual Dissolution Results" (eCTD Sequence 0002). Should batch # (b) (4) differ from batch # 17-000591, please submit the detailed 12-unit dissolution release profile data for this formulation (individual, mean, range, %CV, and mean profiles) using the proposed dissolution method".

The Applicant clarified in the email response that The CMC team has clarified that this was a typographic error in the response. In the first sentence, it should be batch 17-000591 instead of (b) (4)

The Applicant's response/email to IR item 1 is adequate and acceptable.

List of Deficiencies: None

From the Biopharmaceutics perspective, NDA 211675-ORIG-1 is recommended for approval

Primary Biopharmaceutics Reviewer Name and Date:

Rajesh Savkur, Ph.D.; 5/12/2019

Secondary Reviewer Name and Date:

Haritha Mandula, Ph.D.; 5/12/2019

Tertiary Reviewer Name and Date

Sandra Suarez, Ph.D.; 5/13/2019



Rajesh
Savkur

Digitally signed by Rajesh Savkur
Date: 5/13/2019 09:32:04AM
GUID: 5a4fe3d5001e3750f54a8daadb2faa06



Sandra
Suarez

Digitally signed by Sandra Suarez
Date: 5/13/2019 11:08:58AM
GUID: 5033874b000046a4a8b9c51d6f5bd8ba



Haritha
Mandula

Digitally signed by Haritha Mandula
Date: 5/13/2019 04:06:11PM
GUID: 508da6fb000282df41459408f32a1ce0



Pratibha
Bhat

Digitally signed by Pratibha Bhat
Date: 5/14/2019 04:58:04PM
GUID: 59aee75400778a5d31ac2cae7a0e9c5c



Joanne
Wang

Digitally signed by Joanne Wang
Date: 5/14/2019 06:28:49PM
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Final Risk Assessment – NDA 211675 Upadacitinib ER Tablets

DP attribute/ CQA	Factors that may impact the CQA	O ¹	S ^{1,2}	D ¹	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations or comments
Appearance	<ul style="list-style-type: none"> Package permeability Tableting 	1	3	3	9	(b) (4)	9	N/A
Identity	<ul style="list-style-type: none"> incorrect drugs formulated no drug formulated incorrect (b) (4) API 	1	3	2	6	<ul style="list-style-type: none"> Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substance includes several non-specific identification tests (HPLC retention, UV absorption spectrum), consistent with Q6A Severity of failure would depend on situation (incorrect or no drug present)² (b) (4) required under API specification (b) (4) 	6	N/A
Assay	<ul style="list-style-type: none"> input purity of API (b) (4) (b) (4) incorrect amounts of API formulated impurity formation due to interaction of drugs with excipients or catalyzed by excipients degradation of drug substance as formulated (b) (4) 	2	3	2	12	<ul style="list-style-type: none"> Total impurities allowed in input API limited by respective specification (b) (4) GMP adherence should prevent incorrect API/excipient amounts formulated Compatibility of API with excipients generally demonstrated by stability data (b) (4) 	12	N/A
Purity	<ul style="list-style-type: none"> input purity of API impurity formation due to interaction of drugs with excipients or catalyzed by excipients 	2	3	3	18	<ul style="list-style-type: none"> Total impurities allowed in input API limited by respective specification (b) (4) Compatibility of API with excipients generally demonstrated by stability data (b) (4) 	18	N/A

¹ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

² Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of “3” was used throughout)

Final Risk Assessment – NDA 211675 Upadacitinib ER Tablets

	<ul style="list-style-type: none"> degradation of drug substance as formulated 								
Dissolution	<ul style="list-style-type: none"> (b) (4) (b) (4) variability (b) (4) variable (b) (4) variable (b) (4) variable (b) (4) package permeability (b) (4) variable (b) (4) 	2	3	3	18	<ul style="list-style-type: none"> (b) (4) (b) (4) found to have minimal impact on dissolution (b) (4) an additional specification requirement was added for this excipient (b) (4) had limited impact on dissolution rate (b) (4) found to have little impact on dissolution (b) (4) Dissolution did not change (b) (4) (b) (4) did not lead to dissolution failures (b) (4) (b) (4) limited change in the dissolution profile 	18	N/A	
Uniformity of Dosage Units	<ul style="list-style-type: none"> (b) (4) variable (b) (4) (b) (4) (b) (4) 	2	3	4	24	<ul style="list-style-type: none"> (b) (4) (b) (4) Applicant claims (b) (4) Applicant states (b) (4) (b) (4) Content uniformity is tested as part of drug product 	24	N/A	

Final Risk Assessment – NDA 211675 Upadacitinib ER Tablets

(b) (4)	<ul style="list-style-type: none"> (b) (4) permeability 	2	3	3	18	specification as per USP <905> <ul style="list-style-type: none"> Applicant has (b) (4) 	18	N/A
Microbial limits	<ul style="list-style-type: none"> microbial load of input materials for formulation microbial contamination (b) (4) microbial growth during shelf life 	1	3	3	9	<ul style="list-style-type: none"> Applicant claims that the microbiological quality is controlled by the specifications of the incoming formulation components and in general, by application of cGMPs The CCS is said to assure there will be no contamination of the drug product during its shelf life (b) (4) Stability batches will not be routinely tested for microbial limits 	9	N/A



Craig
Bertha

Digitally signed by Craig Bertha

Date: 5/15/2019 09:23:59AM

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