CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213801Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213801
MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension)

Assessment #1

Drug Product Name	MYRBETRIQ Granules (mirabegron for extended-release oral suspension)
Dosage Form	For extended-release oral suspension
Strength	8 mg / mL after reconstitution
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Astellas Pharma Global Development, Inc.
US agent, if applicable	Not Applicable

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission (0001)	09/28/2020	All
Amendment (0004)	10/29/2020	Drug Substance, Drug Product
Amendment (0005)	10/30/2020	Biopharmaceutics
Amendment (0006)	11/06/2020	OPMA
Amendment (0007)	12/11/2020	Micro; Drug Product
Amendment (0009)	12/15/2020	Drug Product
Amendment (0014)	12/22/2020	Biopharmaceutics; Drug Product
Amendment (0021)	01/15/2021	Drug Product
Amendment (0024)	01/26/2021	OPMA; Drug Product
Amendment (0025)	02/05/2021	Drug Product
Amendment (0026)	02/09/2021	OPMA, Drug Product
Amendment (0028)	02/19/2021	OPMA; Drug Product
Amendment (0030)	03/04/2021	OPMA, Drug Product, Biopharmaceutics
Amendment (0031)	03/04/2021	Drug Product
Amendment (0032)	03/05/2021	Drug Product
Amendment (0036)	03/17/2021	Drug Product
Amendment (0037)	03/19/2021	Drug Product
Amendment (0038)	03/23/2021	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sukhamaya (Sam) Bain	Donna Christner
Drug Product	Mark Seggel	Wendy Wilson-Lee
Manufacturing Process	Yong Wu	Yubing Tang
Facilities	Yong Wu	Yubing Tang
Microbiology	Jason God	Julie Nemecek
Biopharmaceutics	Assadollah Noory	Vidula Kolhatkar
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Hong Cai	
Laboratory (OTR)	-	-
Environmental	Mark Seggel	Wendy Wilson-Lee
Labeling	Mark Seggel	Wendy Wilson-Lee

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Astellas Pharmaceuticals' 505(b)(2) New Drug Application 213801, for MYRBETRIQ Granules (mirabegron for extended-release oral suspension), 8 mg/mL of mirabegron after reconstitution, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product.

The prescribing information (PI) and patient package insert (PPI) as submitted on March 23, 2021 (0038) and the labels as submitted on March 17, 2021 (0036) and March 19, 2021 (0037) are accurate, complete and comply with the requirements under 21 CFR 201.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 17, 2021. The recommendation remains current as of this review.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed drug product Myrbetriq Granules (mirabegron for extended-release oral suspension) is a new formulation of mirabegron developed for the treatment of neurogenic detrusor overactivity (NDO) for the pediatric patients aged 3 years and older. The active ingredient mirabegron is a beta-3 adrenergic agonists and approved in the US under Myrbetriq (mirabegron extended-release tablets), 25 mg and 50 mg, in June 28, 2012 (NDA 202611) for the adult patients and for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. Myrbetriq and Myrbetriq Granules are not substitutable on a milligram-per-milligram basis.

MYRBETRIQ Granules is supplied as granules in multi-dose bottles that are packaged in the aluminum pouches with desiccant. Each bottle is filled with approximately 8.3 g of yellowish white granules, which contain 830 mg of mirabegron. After reconstitution with 100 mL water, Myrbetriq Granules is pale brownish yellow to yellow oral suspension with 8 mg/mL of mirabegron. The oral suspension can facilitate the recommended

dosage which is determined based on patient weight. The liquid formulation will provide an alternative to the tablets for pediatric patients who have difficulties swallowing the tablets. (b) (4) This is considered crucial for the pediatric patients. Myrbetriq Granules has an extended-release profile. This is the result of its formulation (b) (4)

The preparation of the suspension will be performed by pharmacists at the time of dispensing to the patients. The pharmacist should also provide an appropriate oral dosing device to the patient. The instructions for reconstitution of Myrbetriq Granules by the pharmacist and the instructions for patient use are driven by the physico-chemical properties of the drug product. From the CMC perspective, the instructions for pharmacists and patients in the Prescribing Information (PI) and Patient Package Insert (PPI) are adequate to ensure the quality of the delivered doses.

The manufacturing, primary packaging and release testing of MYRBETRIQ Granules will be conducted at Astellas Pharm Tech Co., Ltd. Located at Yaizu-shi, Japan. The final packaging, labeling and release testing will be conducted at Astellas Pharma Europe B. V., Meppel, The Netherlands.

The expiration dating period is 24 months when MYRBETRIQ Granules is stored at 20ºC to 25ºC (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. The maximum patient use period is 28 days after reconstitution with water when stored at 20ºC to 25ºC.

Proposed Indication(s) including Intended Patient Population	for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older.
Duration of Treatment	As needed
Maximum Daily Dose	80 mg (10 mL)
Alternative Methods of Administration	Not Applicable

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance mirabegron is a white crystalline powder, practically insoluble in water, but soluble in dimethyl sulfoxide. It melts at about 144 °C. Its two significant pKa's are at 4.5 (thiazol -NH2) and 8.0 (amine -NH). It is not hygroscopic. Two polymorphic forms have been identified, the (b) (4) form is the drug substance.

The applicant cross-references NDA 202611 for practically all mirabegron drug substance information. The original NDA 202611 was approved on June 28, 2012. All API-related supplements to NDA 202611 have been approved by the Agency – the latest one was on January 22, 2021.

The drug substance batch data submitted in the present NDA 213801 on October 29, 2020 are within the current specification in the cross-referenced NDA 202611, which includes 4 impurities which are at not more than the ICH M7 TTC of 30 ppm.

There are three suppliers of the drug substance, mirabegron: Astellas Pharma located at Takahagi-shi, Japan; Astellas Ireland Co., Ltd. located at Mulhuddart, Ireland, and (b) (4) . The retest period is (b) (4) for Mirabegron when stored at (b) (4) .

The drug substance reviewer Dr. Sukhamaya (Sam) Bain finds the information on the drug substance mirabegron is adequate to support the approval of the NDA. See IQA Chapter Drug Substance I for details.

Drug Product: Adequate

MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension) is supplied as the (b) (4) non-sterile and non-aqueous granules which contains the (b) (4) active ingredient mirabegron and (b) (4) diluted hydrochloric acid, xanthan gum, hypromellose, mannitol, magnesium stearate, acesulfame potassium, methylparaben, ethylparaben, simethicone, and silicon dioxide. All excipients are of compendial grade and acceptable from the quality perspective.

The specification includes the tests, analytical procedures and acceptance criteria, necessary to ensure the identity, strength, quality, purity and bioavailability of the drug product. (b) (4) The microbiological contamination is controlled by the testing of microbial limit and the assays of (b) (4) . A within-bottle uniformity is included to demonstrate the suspendability and the dose accuracy for this

suspension packaged in the multi-dose container. The dissolution test is included for quality control of the extended-release formulation (see IQA Chapter VI Biopharmaceutics). Other tests include related substances, pH and (b) (4) The proposed acceptance criteria for all the attributes are acceptable from the quality perspective. (b) (4) The applicant's proposal of not including the test for the (b) (4) elemental impurities in drug product release specification is acceptable per ICH (b) (4) and Q3D, respectively.

The batch data for the registration batches as well as supportive clinical batches all conform to the specifications. The analytical methods used in analysis of the drug product batches, at release and in stability studies, were suitably validated and deemed adequate for the intended purpose.

MYRBETRIQ Granules is supplied as granules in bottles packaged in an aluminum pouch with desiccant. Each bottle is filled with approximately 8.3 g of granules, which contain 830 mg of mirabegron. The reconstituted suspension will be prepared by the pharmacists and stored in the same bottle. The suitability of the container closure system has been demonstrated through the appropriate long-term, accelerated, and photostability studies.

The stability data support the proposed expiration dating period of 24 months when MYRBETRIQ Granules is stored at 20ºC to 25ºC with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] in the proposed container closure system. The applicant has provided adequate data to support the 28 days patient use period when stored at 20ºC to 25ºC after the reconstitution with water.

The applicant has requested a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b). Astellas states that there are no extraordinary circumstances associated with the use of mirabegron. The categorical exclusion is granted.

In summary, Dr. Mark Seggel has recommended approval for this application from the drug product perspective. See IQA Chapter II, Drug Product for details.

Labeling: Adequate

During the initial assessment of the labeling (prescribing information (PI), patient package insert (PPI), and container/carton labels), several deficiencies were identified and conveyed to the Applicant with the collaboration with DMEPA and the clinical review team. All of the

previously identified deficiencies have been satisfactorily resolved. The prescribing information (PI) and patient package insert (PPI) as submitted on March 23, 2021 (0038) and the labels as submitted on March 17, 2021 (0036) and March 19, 2021 (0037) are accurate, complete and comply with the requirements under 21 CFR 201.

From the ONDP perspective, this application is deemed ready for approval in its present form per 314.125(b)(8). Refer to IQA Labeling Chapter IV for details.

Manufacturing Integrated Assessment: Adequate

Process: adequate

The manufacturing process for MYRBETRIQ Granules involves the following steps: (b) (4) The size of the registration batches is (b) (4) kg which is the same for the proposed commercial batch size. No (b) (4) are proposed.

The applicant has investigated the critical manufacturing process parameters (e.g. (b) (4) etc.), testing of the critical quality attributes of the drug products (e.g. the (b) (4) content uniformity of mirabegron, (b) (4), pH, preservative assays, particle size distributions and fill weight, etc.). Proper acceptance criteria and the sampling plan has been established. The overall manufacturing process and control is deemed adequate.

Although the assays met the acceptance criteria of the specification, it is noted that the variability in assays for mirabegron and (b) (4) were observed with one of the process performance qualification (PPQ) batches. The applicant proposed to (b) (4) as the mitigation strategy. This potential assay variability concern is further addressed by (b) (4) to ensure the requisite quality and performance of the finished product.

The finished drug product granules are manufactured at Astellas Pharma Tech Co., Ltd. located at Shizuoka, Japan.

Facilities: adequate

Pre-approval inspections (PAI) were conducted via 704(a)(4) due to COVID-19 travel restrictions for the following three facilities: Astellas

Pharma Tech Co., Ltd. Japan (FEI: 3002809620) for the drug product manufacturing; Astellas Pharma Europe B.V. (FEI: 3002808518), The Netherlands for the drug product packaging/labeling, release and stability testing and storage; (b) (4) for the drug substance microbiological testing. Other manufacturing facilities related to the commercialization of the drug product are acceptable based on the compliance history, acceptable profile codes and experience in the proposed responsibilities to support this application.

The OPMA reviewer, Dr. Yong Wu, has concluded that the overall manufacturing process, controls and the facilities are adequate to support the approval of this NDA from OPMA perspective. See IQA OPMA Chapter V for manufacturing process and facilities for details.

Biopharmaceutics: Adequate

The control of the mirabegron release is based on [redacted]. The following two step dissolution testing method and the acceptance criteria has been established for the routine quality control (QC) of the drug product Myrbetriq Granules at batch release and during stability testing:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
2	100	Step 1: 0.036 mol Phosphate buffer pH 6.8 at 37±0.5°C Step 2 (after 4 hours): 0.108 mol Phosphate buffer pH 6.8 at 37±0.5°C	500 500	15 min: [redacted]% 2 h: [redacted]% 8 h: NLT [redacted]%

This 2-step method utilizes 500 mL of pH 6.8 USP phosphate buffer that contains 0.036 mol [redacted] (step 1), which is followed by the addition of 500 mL of 0.108 mol (step 2) to obtain almost complete release of mirabegron. Note that the [redacted] concentration added in the step 2 is three times as that in the step 1 phosphate buffer medium. Dissolution data from clinical batches and registration batches support the proposed dissolution acceptance criteria. Different particle sizes of mirabegron or [redacted] did not significantly affect the dissolution rate of mirabegron from MYRBETRIQ Granules. However, the dissolution profile is faster with [redacted] particle size. The biopharmaceutics information provided in this application has been reviewed by Dr. Assadollah Noory and concluded the dissolution method is adequate for the quality control.

The applicant has studied the impact of the dissolution rate of mirabegron from MYRBETRIQ Granules with the addition of alcohol (alcohol dose dumping study). The addition of alcohol (5, 10, 20, and 40%) increases the dissolution rate of mirabegron from MYRBETRIQ Granules at pH 6.8, but there is no increase at pH1.0. This study results have been communicated to the clinpharm review team.

Dr. Assad has recommended the approval of this application from biopharmaceutics perspective. See IQA Biopharmaceutics Chapter VI for details.

Microbiology (if applicable): Adequate

MYRBETRIQ Granules is manufactured as a [redacted] non-sterile and non-aqueous drug product. However, it is reconstituted with water as a suspension in the primary container closure system at the time of dispensing to the patient by the pharmacist.

The applicant has provided the microbial limits testing of TAMC and TYMC per USP<61> and E. coli per USP<62> in mirabegron granules release and stability specification. The proposed microbial limits and testing procedures comply with regulatory expectations for a non-aqueous, oral product.

The (b) (4) of the reconstituted suspension was assayed at the time of reconstitution and at the end of the 28 day in-use period and the results met the specification. (b) (4) effectiveness for the duration of the 28-day in-use period has been shown at the minimum label claim (b) (4).

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the drug product and 28-day patient in-use period of the reconstituted suspension when stored at the proposed condition in the product labeling.

The microbiology information submitted in this application has been reviewed by the microbiology reviewer Dr. Jason God who has found the information provided in the application adequate to support the approval of this application from the microbiology perspective. See the detailed review from Dr. Jason God in the Microbiology Chapter VII of the IQA.

FACILITY STATUS REPORT AND OVERALL RECOMMENDATION
As of 03/24/2021

C. Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Identification	L	Granules; Reconstituted suspension; drug product specification	L	
Assay	L	(b) (4) drug product specification	L	
Dose Uniformity	M	(b) (4) via drug product specification	L	Suspendability and uniformity of suspension demonstrated; IFU details steps to ensure homogeneity prior to dosing
Related Substances	L	Formulation with (b) (4) and drug product specification	L	
Dosing Accuracy	M	Formulation, Manufacturing process and drug product specification; In-use stability study	L	Not a narrow therapeutic index drug, but dosing remains dependent on user
Content Uniformity	M	(b) (4)		
PSD of the granules	M	(b) (4)	L	
Dissolution	M	Formulation, Manufacturing process and drug product specification; In-use stability study. (b) (4)	L	In vivo release rate (b) (4)

Alcohol Dose Dumping (extended-release formulation)	M	In vitro release rate increase at pH 6.8 but NOT in 0.1 N HCl;	L	Formulation primarily for pediatric patients;
pH	L	control via specification	L	
(b) (4) Assay	M	Formulation development and control via (b) (4) the drug product specification	L	
Microbial Limits	L (granules) M (reconstituted suspension)	control via specification In-use stability study	L	
Leachables	M	Risk assessment per USP<1664>; Oral use only. Long-term storage of solid granules; but reconstituted suspension NMT 28 days.	L	

Lifecycle Management Considerations

Any proposed change to component quality, formulation or manufacturing process should be carefully assessed for impact on (b) (4) and on the in vitro dissolution profile should be carefully addressed under both long-term storage conditions and in-use.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

na

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

8. Other Deficiencies (Specify discipline, such as Environmental)

na

Application Technical Lead Name and Date:

Hong Cai, Ph.D.
CMC Lead (acting)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		NA	NA	
	III			NA	NA	
	III			NA	NA	

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed during the current review cycle.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND submissions, associated reviews, and communications	IND 069416	Investigational use of Mirabegron for the treatment of an overactive bladder
NDA application(s)	NDA 202611	Myrbetriq (mirabegron extended-release tablets), 25- and 50-mg; Astellas; AP 06/28/2012

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH-ODE	na			
CDRH-OC	na			

Clinical	na			
Other	na			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (see Chapter II)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology

CHAPTER VIII: Additional Quality Disciplines *Not applicable*

Hong Cai

Digitally signed by Hong Cai
Date: 3/24/2021 04:03:16PM
GUID: 55919d6500e16bdaad5825645e4f22ff

40 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

MYRBETRIQ Granules (mirabegron for extended-release oral suspension) is supplied as granules in multi-dose bottles that are packaged in aluminum pouches with desiccant. After reconstitution with 100 mL of water by the pharmacist, the oral suspension has 8 mg/mL mirabegron. Unused suspension should be discarded after 28 days. This labeling review covers the CMC-related sections of the prescribing information (PI), the carton label, bottle label, and the aluminum pouch label.

Note that the prescribing information has been designed to cover both MYRBETRIQ Granules (mirabegron for extended-release oral suspension) and MYRBETRIQ (mirabegron extended-release tablets). (MYBETRIQ was approved under NDA 202611; see also efficacy supplement S-017, which is currently under review for the treatment of NDO in pediatric patients, and the associated CMC review.)

This assessment is based on the revised PI submitted on March 23, 2021 (SN0038). The labeling review team (ONDP, OPPQ, DMEPA and clinical) has provided the comments to the applicant on January 29, 2021, February 23 and 24, 2021, and March 17, 18, and 22, 2021. The following submissions were reviewed:

Labeling Submissions Assessed	Document Date
Original Submission (SN0001)	September 28, 2020
Amendment (SN0009)	December 15, 2020
Amendment (SN0031)	March 04, 2021
Amendment (SN0032)	March 05, 2021
Amendment (SN0036)	March 17, 2021
Amendment (SN0037)	March 19, 2021
Amendment (SN0038)	March 23, 2021

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	MYRBETRIQ GRANULES	**Satisfactory**
Established name(s)	(mirabegron for extended-release oral suspension)	**Satisfactory**
Route(s) of administration	oral	**Satisfactory**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For extended-release oral suspension: 8 mg/mL of mirabegron after reconstitution	**Satisfactory**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	na	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	na	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See proposed Section *"2.6* (b) (4) *"* above copied from the proposed PI.	**Satisfactory**

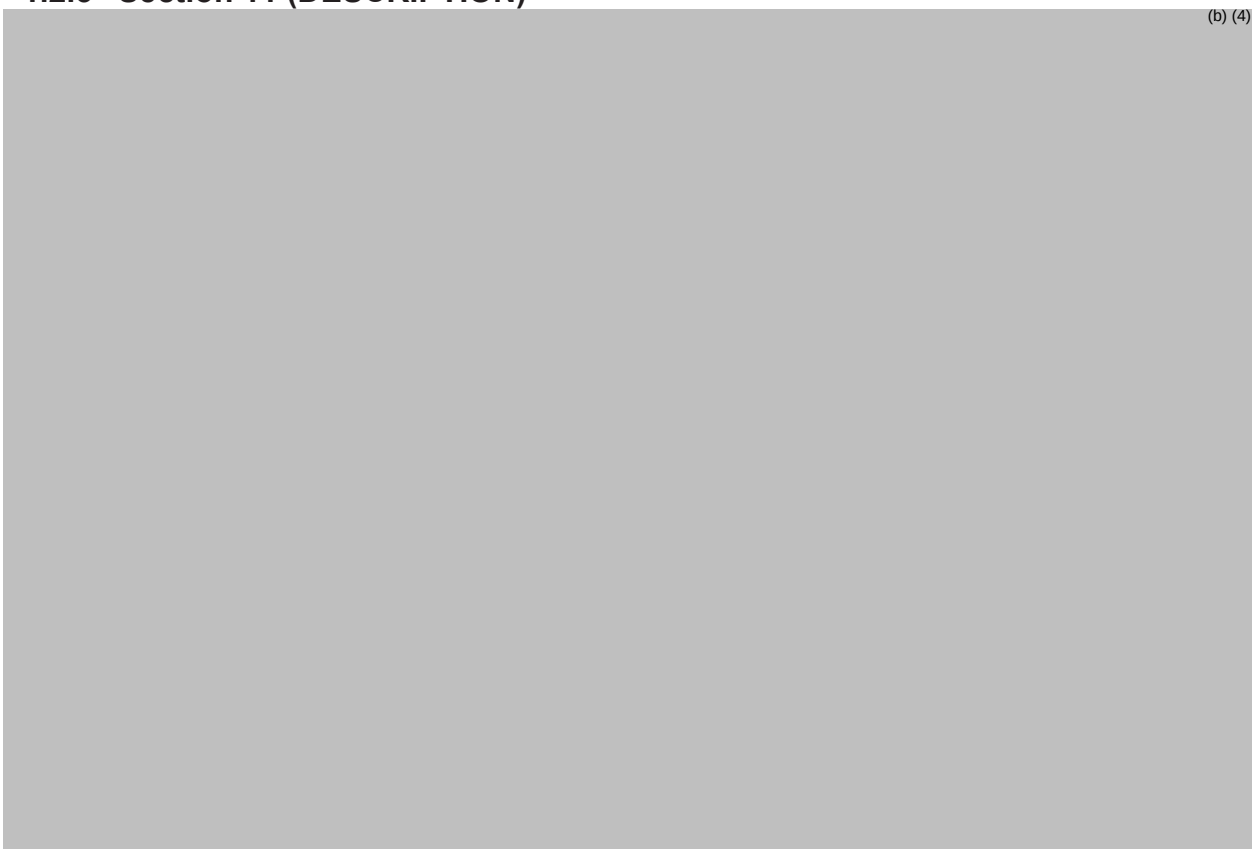
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

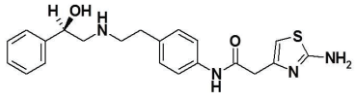
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	for extended-release oral suspension	**Satisfactory**
Strength(s) in metric system	8 mg/mL of mirabegron	**Satisfactory**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	na	na
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	yellowish white granules After reconstitution with 100 mL water, the oral suspension is pale brownish yellow to yellow with 8 mg/mL of mirabegron	**Satisfactory**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	na	na
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	na	na

1.2.3 Section 11 (DESCRIPTION)

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	MYRBETRIQ Granules (mirabegron for extended-release oral suspension)	**Satisfactory**
Dosage form(s) and route(s) of administration	for extended-release oral suspension	**Satisfactory**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	na	na
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	acesulfame potassium, diluted hydrochloric acid, ethylparaben, hypromellose, magnesium stearate, mannitol, methylparaben, silicon dioxide, simethicone, sodium polystyrene sulfonate, and xanthan gum	**Satisfactory**
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		**Satisfactory**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	na	na
Statement of being sterile (if applicable)	na	na
Pharmacological/ therapeutic class	beta-3 adrenergic agonist	**Satisfactory**

Chemical name, structural formula, molecular weight	The chemical name of mirabegron is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide having an empirical formula of C21H24N4O2S and a molecular weight of 396.51. The structural formula of mirabegron is: 	**Satisfactory**
If radioactive, statement of important nuclear characteristics.	na	na
Other important chemical or physical properties (such as pKa or pH)	Mirabegron is a white powder. It is practically insoluble in water (0.082 mg/mL). It is soluble in methanol and dimethyl sulfoxide.	**Satisfactory**

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	na	na
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	na	na

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	for extended-release oral suspension	**Satisfactory**
Strength(s) in metric system	8 mg/mL of mirabegron	**Satisfactory**
Available units (e.g., bottles of 100 tablets)	Each bottle is filled with approximately 8.3 g of granules, which contain 830 mg of mirabegron. After reconstitution with 100 mL water, the oral suspension is pale brownish yellow to yellow with 8 mg/mL of mirabegron.1 Carton Containing 1 Bottle	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Each bottle is filled with approximately 8.3 g of yellowish white granules, which contain 830 mg of mirabegron. After reconstitution with 100 mL water, the oral suspension is pale brownish yellow to yellow with 8 mg/mL of mirabegron.	**Satisfactory**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	na	na
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	na	na

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	na	**na**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	na	na
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store MYRBETRIQ Granules at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store the reconstituted suspension at 20°C to 25°C (68°F to 77°F) for up to 28 days. Discard the unused portion after 28 days.	**Satisfactory**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	na	na

Include information about child-resistant packaging		

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Marketed and Distributed by: **Astellas Pharma US, Inc.** Northbrook, IL 60062	**Satisfactory**

2.0 PATIENT LABELING

Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

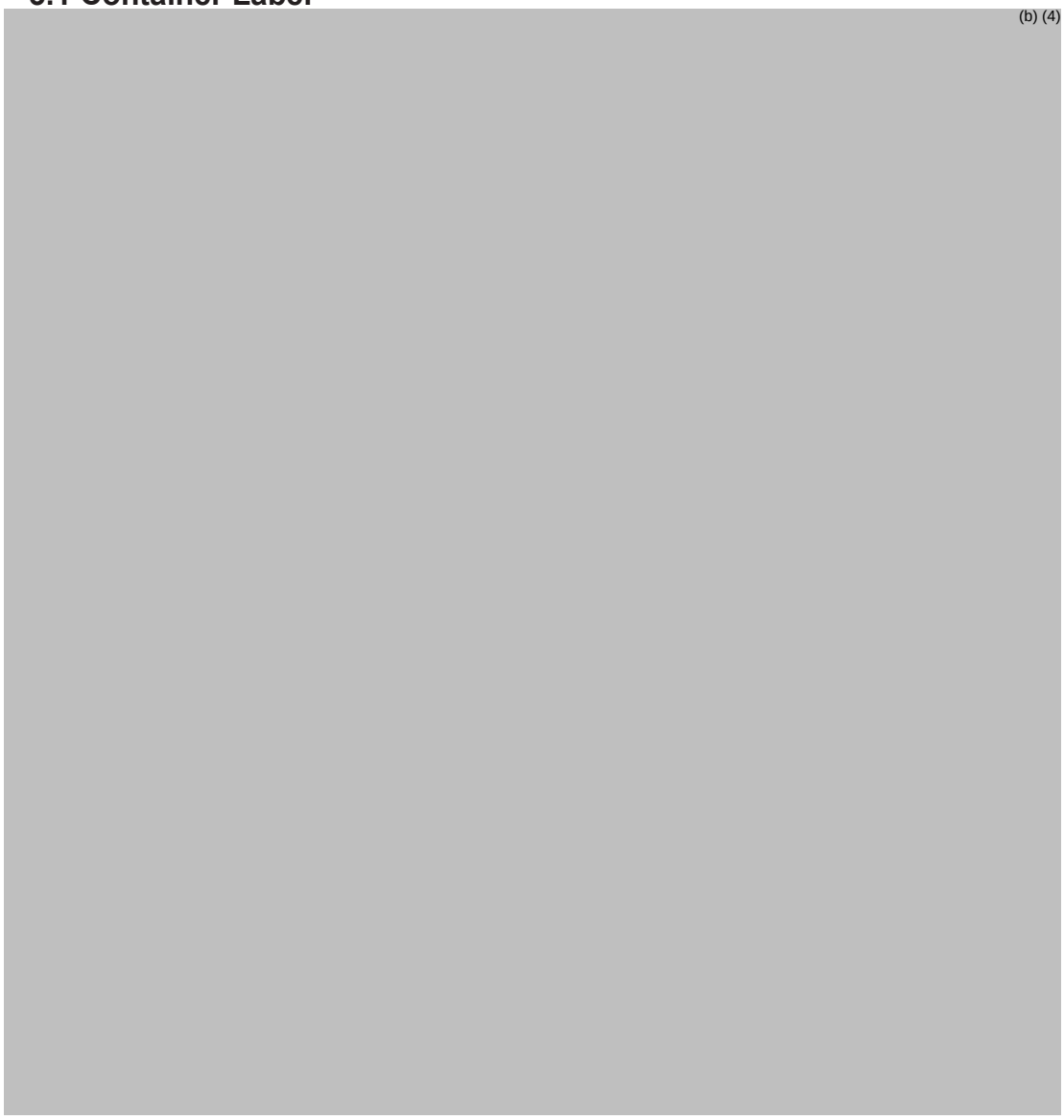
Satisfactory

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

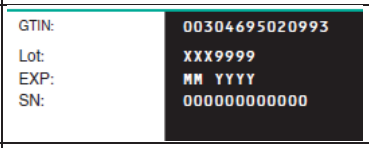
3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Myrbetriq® Granules (mirabegron for extended-release oral suspension)	**Satisfactory**
Dosage strength	8 mg/mL	**Satisfactory**
Route of administration	for extended-release oral suspension	**Satisfactory**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	na	na
Net contents (e.g. tablet count)	100 mL	**Satisfactory** (ca. 103.5 mL after reconstitution with 100 mL water) (ca. 8.3 g granules containing 830 mg mirabegron)
"Rx only" displayed on the principal display panel	Rx only	**Satisfactory**
NDC number	NDC 0469-5020-99	**Satisfactory**
Lot number and expiration date		**Satisfactory**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store Myrbetriq® Granules at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. • Store the reconstituted suspension at 20°C to 25°C (68°F to 77°F) for up to 28 days. • Discard the unused portion after 28 days.	**Satisfactory**

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	na	na
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	na	na
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	na	na
Bar code	provided	**Satisfactory**

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Marketed by: **Astellas Pharma US, Inc.** Northbrook, IL 60062	**Satisfactory**
Medication Guide (if applicable)	na	na
No text on Ferrule and Cap overseal	na	na
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	na	na
And others, if space is available	na	

Assessment of Carton and Container Labeling: *adequate.*

The assessment is based on the carton and container labels submitted in SN0036 dated March 17, 2021 (aluminum pouch) and in SN0037 dated March 19, 2021 (Carton and Bottle). Note that the aluminum foil pouch label does not include the statements of the strength, Rx only and the net content. The pouch is for storage of the product only and is not to be dispensed. Per DMEPA reviewer Denis Baugh, it should not include drug identifying information (the Rx only, strength, and net content) which would suggest that it should be a part of the dispensing process. Refer to her email response on March 18, 2021.

ITEMS FOR ADDITIONAL ASSESSMENT

na

List of deficiencies from initial assessments:

A. Prescribing Information:

1. Revise labeling to reflect the new proprietary name MYRBETRIQ Granules.
2. The dosage form is “for extended-release oral suspension”.
3. Revise “Dosage Forms and Strengths” in the Highlights Section to the following: “For extended-release oral suspension: 8 mg/mL of mirabegron after reconstitution”.
4. Revise “Section 3 Dosage Forms and Strengths” to the following: “MYRBETRIQ Granules (mirabegron for extended-release oral suspension): Each bottle is filled with approximately 8.3 g of yellowish white granules, which contain 830 mg of mirabegron. After reconstitution with 100 mL water, the oral suspension is pale brownish yellow to yellow with 8 mg/mL of mirabegron.”
5. In Section 11 Description:
    a. Add the information that MYRBETRIQ Granules (mirabegron for extended-release oral suspension) is beta-3 adrenergic agonists.
    b. Add the established name for MYRBETRIQ Granules
    c. Revise the list of the inactive ingredients for MYRBETRIQ Granules in alphabetical order per current labeling practice.
    d. Add the reconstituted suspension strength as the following to the paragraph of MYRBETRIQ Granules description information “After reconstituted with 100 mL water, the suspension contains 8 mg/mL of mirabegron”.

6. In Section 16 How Supplied/Storage And Handling,
    a. (b) (4) the identification characteristics and the strength of the granules (b) (4) and add that information in the text.

b. Add the reconstituted suspension strength and the identification characteristics of MYRBETRIQ Granules: “After reconstitution with 100 mL water, the oral suspension is pale brownish yellow to yellow with 8 mg/mL of mirabegron.”
c. There is insufficient data to support (b) (4) for the reconstituted suspension. Revise the storage condition of the reconstituted suspension to the following: “Store the reconstituted suspension at 20°C to 25°C (68°F to 77°F) for up to 28 days. Discard the unused portion after 28 days.”

B. Carton and Container Labels:

1. General Comments (applicable to all labels)

a. Revise the carton and container labels to be consistent with the comments in PI for the dosage form, storage condition.

Overall Assessment and Recommendation:

All of the previously identified deficiencies have been satisfactorily resolved. The labels as submitted on March 17, 2021 (0036) and March 19, 2021 (0037) are accurate, complete and comply with the requirements under 21 CFR 201. The prescribing information (PI) and patient package insert (PPI) as submitted on March 23, 2021 (0038) are likewise accurate, complete and comply with the requirements under 21 CFR 201. From the ONDP perspective, this application is deemed ready for approval in its present form per 314.125(b)(8).

Primary Labeling Assessor Name and Date:
Mark R. Seggel, Ph.D.
Chemist
OPQ/ONDP/DNDPII/Br4

{see electronic signature page}

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Wendy Wilson-Lee, Ph.D.
Division Director
OPQ/ONDP/DNDPII

{see electronic signature page}

Mark Seggel

Digitally signed by Mark Seggel
Date: 3/23/2021 04:48:42PM
GUID: 507572b50000361769693561480 25bae

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 3/23/2021 04:58:53PM
GUID: 50816dbc000085595ca3284bbca465a8

55 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background: Mirabegron is a beta-3 adrenergic agonist, indicated for the treatment of overactive bladder (OAB) in adults with symptoms of urge urinary incontinence, urgency, and urinary frequency. It is currently approved under NDA 202611 Myrbetriq® 25 mg and 50 mg tablets. Granules, 8 mg/mL, for oral suspension for pediatric use 3 years and up is the subject of this NDA.

NDA: 213801-ORIG-1

Drug Product Name / Strength:
Myrbetriq (b) (4) (Mirabegron), Granules, 8 mg/mLfor suspension

Route of Administration: Oral

Applicant Name: Astellas Pharma Global Development, Inc.

Review recommendation:
From a biopharmaceutics' perspective this NDA is recommended for approval.

Review Summary:
The proposed indication for mirabegron 8 mg/mL oral suspension is the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older. The extended-release granules are reconstituted with water to prepare a mirabegron 8 mg/mL oral suspension. In support of biopharmaceutics section of the NDA the Applicant provided dissolution method development and dissolution data from clinical and registration batches. Initially the Applicant had not provided data from alcohol dose dumping as the product is indicated for pediatric use. However, following a request for information, the Applicant generated the alcohol dose dumping dissolution data. The submitted data are adequate in meeting biopharmaceutics requirement of the NDA. The approved dissolution method and acceptance criteria is shown below.

Approved dissolution test method and acceptance criteria:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
2	100	Step 1: 0.036 mol Phosphate buffer pH 6.8 at 37±0.5°C Step 2 (after 4 hours): 0.108 mol Phosphate buffer pH 6.8 at 37±0.5°C	500 500	15 min: (b) (4)% - (b) (4)% 2 h: (b) (4)% - (b) (4)% 8 h: NLT (b) (4)%

List Submissions being reviewed:

Document(s) Assessed	Date Received
Original submission	09/28/2020
Response to Information Request	10/30/2020
Response to Information Request	12/22/2020

Highlight Key Outstanding Issues from Last Cycle:

This is the first cycle of review.

Concise Description Outstanding Issues Remaining:

No issue is outstanding.

BCS Designation

Reviewer's Assessment:

BCS classification is not provided.

Solubility:

Permeability:

Dissolution method:

(b) (4)

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Acceptance criteria:

To set the acceptance criteria, multi-point dissolution data of Phase 3 clinical trial materials and registration batches were used shown below.

Table 14 Dissolution Data of Phase 3 Clinical Trial Material and Registration Batches using Proposed Dissolution Test Method (n = 12 Vessels)

Sampling Time	Phase 3 Clinical batch		Registration batch			Mean
	Lot No. 16036A initial	Lot No. 16S0210A 25°C/60%RH 36M	Lot No. 18072G initial	Lot No. 18073H initial	Lot No. 18074G initial	
15 min.	30.5%	30.4%	31.8%	31.0%	31.5%	31.0%
	RSD: 2.3%	RSD: 1.5%	RSD: 1.1%	RSD: 2.2%	RSD: 1.0%	
2 hrs.	54.1%	53.8%	55.3%	54.1%	55.2%	54.5%
	RSD: 1.8%	RSD: 1.5%	RSD: 1.3%	RSD: 2.5%	RSD: 1.4%	
4 hrs.	60.2%	60.2%	61.7%	59.9%	61.6%	60.7%
	RSD: 1.1%	RSD: 0.9%	RSD: 1.1%	RSD:1.4%	RSD: 1.0%	
6 hrs.	84.2%	84.4%	86.0%	83.4%	86.0%	84.8%
	RSD: 0.6%	RSD: 0.5%	RSD: 0.9%	RSD: 0.7%	RSD: 0.5%	
8 hrs.	86.0%	86.0%	87.7%	85.3%	87.6%	86.5%
	RSD: 0.5%	RSD: 0.5%	RSD: 0.9%	RSD: 0.7%	RSD: 0.6%	
10 hrs.	86.4%	86.1%	88.1%	85.8%	87.9%	86.9%
	RSD: 0.5%	RSD: 0.6%	RSD: 0.9%	RSD: 0.7%	RSD: 0.5%	
24 hrs.	87.3%	87.0%	89.3%	86.4%	88.7%	87.7%
	RSD: 0.5%	RSD: 0.5%	RSD: 1.0%	RSD: 0.8%	RSD: 0.7%	

(b) (4)

The proposed acceptance criteria were based on the dissolution data from the clinical and registration batches. The Proposed dissolution test and dissolution acceptance criteria is show below.

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
2	100	Step 1: 0.036 mol Phosphate buffer pH 6.8 at 37±0.5°C Step 2 (after 4 hours): 0.108 mol Phosphate buffer pH 6.8 at 37±0.5°C	500 500	15 min: (b) (4)% - (b) (4)% 2 h: (b) (4)% - (b) (4)% 8 h: NLT (b) (4)%

Reviewer's Assessment:

Dissolution data from clinical batches (see appendix) and registration batches support the proposed dissolution acceptance criteria, thus, the dissolution test and the acceptance criteria are acceptable.

Effect of Mirabegron Particle Size:

The effect of particle size of mirabegron on dissolution, mirabegron granules for oral suspension were manufactured by using extremely large or small particle size of mirabegron, and their dissolution properties were evaluated.

Table 8 Effect of Mirabegron Particle Size on Dissolution

(b) (4)

a) Test conditions: USP pH6.8 phosphate buffer, paddle method (b) (4) rpm, 6 vessels

Reviewer's Assessment:

Different particle sizes of mirabegron did not significantly affect the dissolution of mirabegron granules for oral suspension.

Effect of Particle Size of (b) (4)

The effect of particle size of (b) (4) on Mirabegron granules suspension dissolution was evaluated.

Table 9 Effect of (b) (4) Particle Size on Dissolution

(b) (4)

Reviewer's Assessment:

Particle size of (b) (4) showed no significant difference in dissolution of mirabegron.

Effect of (b) (4) Particle Size:

The 1st step of the proposed dissolution method (USP apparatus 2 with rotation speed 100 rpm in 500 mL pH 6.8 USP phosphate buffer) was established to confirm the modified release profile for this product; therefore, (b) (4) small, medium, amd large particle sizes were used, shown below.

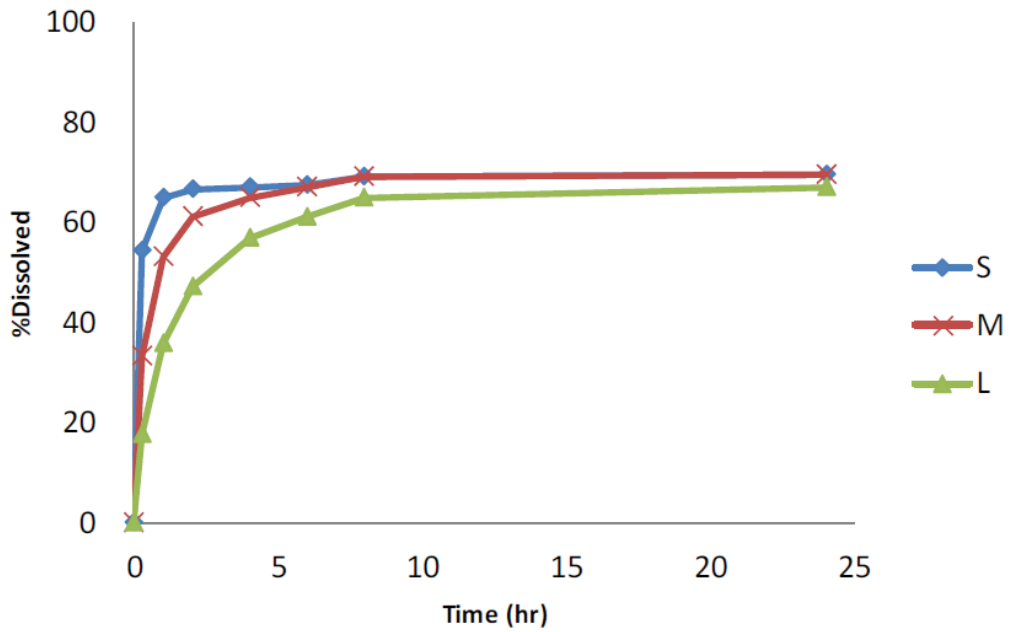
Table 9 Investigation Condition of Discriminatory Power ((b) (4) particle size)

Sample (Lot No.)	Particle size of (b) (4)	Dosing amount (volume)	Paddle rotation Speed	Test medium	Replicates	Sampling time
(b) (4) (ED178-180726-S)	(b) (4) µm pass	24 mg (3 mL)	100 rpm	pH 6.8 USP phosphate buffer 500 mL	n=3 vessels	7 time points 1st: 15 min. 2nd: 1 hr. 3rd: 2 hrs. 4th: 4 hrs. 5th: 6 hrs. 6th: 8 hrs. 7th: 24 hrs.
(b) (4) (ED178-180726-M)	µm on µm pass					
(b) (4) (ED178-180726-L)	µm on					

Table 10 Summary of Preliminary Batch Data (Dissolution, pH 6.8 USP Phosphate Buffer, Dose: 24 mg)

Sample	Sampling Time	Lot No. ED178-180726-S	Lot No. ED178-180726-M	Lot No. ED178-180726-L
(b) (4)	15 min.	54.5%	33.1%	17.7% (b) (4)
	1 hr.	64.8%	53.1%	35.8% (b) (4)
	2 hrs.	66.4%	60.9%	47.3% (b) (4)
	4 hrs.	66.8%	65.1%	56.7% (b) (4)
	6 hrs.	67.2%	66.9%	61.0% (b) (4)
	8 hrs.	69.1%	69.0%	64.7% (b) (4)
	24 hrs.	69.4%	69.5%	66.9% (b) (4)

Figure 6 Drug Release Behaviors (b) (4) Using Different Particle Size (b) (4) (500 mL of pH 6.8 USP Phosphate Buffer)



Reviewer's Assessment:

The results show that the dissolution profile is fastest with small (b) (4) particle size.

There were concerns raised by the CSO (field investigator) during the facility 704a4 assessment for the drug product manufacturing site (Astellas Pharma tech Co). It was related to the deviation from a PPQ (Process Performance Qualification) batch (Lot #20001). Variability in Assay for mirabegron, and (b) (4) was observed. (b) (4)

To address this concern IR was communicated to the applicant that included the following:

- Request to add particle size distribution test to the final drug product granule specification and (b) (4).
- A risk assessment for the impact of granule particle size distribution on the in vitro dissolution of the finished product, along with all supporting data.

In response to the impact of granule particle size distribution on the in vitro dissolution of the finished product, the Applicant provided (b) (4) granules Particle size distribution from process optimizing lots, shown below.

Table 1 Particle size distribution of the process optimizing lots

Lot No.			G00281E	G00381E	G00481E	G00581E	G00681E	G00781E	G00881E	G00981E	G01081E
(b) (4) granules	Particle size distribution (%)	(b) (4) µm on									(b) (4)
		µm on									
		µm on									
		µm on									
		µm on									
		µm on									
		µm on									
		um on									
	(b) (4)	µm pass									Min / Max
Mean particle size D_{50} (µm)											(b) (4)

Dissolution of granules in (b) (4) mL of pH6.8 phosphate buffer solution using apparatus 2 at (b) (4) rpm is shown below.

Figure 2 Relationship between D_{50} of (b) (4) granules and dissolutions

(b) (4)

Dissolution (%)

Reviewer's Assessment:

The applicant assessed dissolution data for products manufactured with mean granule sizes (D_{50}) (b) (4) µm. The data indicated that granules Particle size does not impact the dissolution profile within the tested range. This range is similar to the proposed acceptance criteria range D_{50} of PSD: (b) (4) µm. Acceptability of this proposed range will be assessed by Drug Product reviewer. Since acceptance criteria will be established for granule particle size, the risk associated with dissolution will be reduced.

In-Vitro Alcohol Dose Dumping:

The in-vitro alcohol dose dumping study was performed under the test conditions according to the FDA's Draft Guidance Bioavailability Studies Submitted in NDAs or INDs - General Considerations (February 2019), in addition to 0.1 mol/L HCl, pH 6.8 phosphate buffer was also tested. See more detail data in appendix.

Dissolution Medium†	Test Method	Alcohol Concentration	Suspension Volume (Strength)	Sampling Time
0.1 mol/L HCl, 900 mL	Paddle apparatus, 100 rpm	0%, 5%, 10%, 20%, 40%	3 mL (24 mg, lowest), 10 mL (80 mg, highest)	15 min, 2 hours, 4 hours
pH 6.8 phosphate buffer (USP), 500 mL + pH 6.8 phosphate buffer (3 times (b) (4) concentration of USP buffer), 500 mL‡				15 min, 2 hours, 4 hours, 6 hours, 8 hours

† These dissolution media were mixed with dehydrated alcohol to make the intended concentration and the presented volume of mixture were added into each vessel.

‡ pH 6.8 phosphate buffer (3 times (b) (4) concentration of USP buffer) was added into vessels after the sampling at 4 hours.

The results are show below.

Figure 1 Dissolution Plots (0.1 mol/L HCl, 3 mL Suspension)

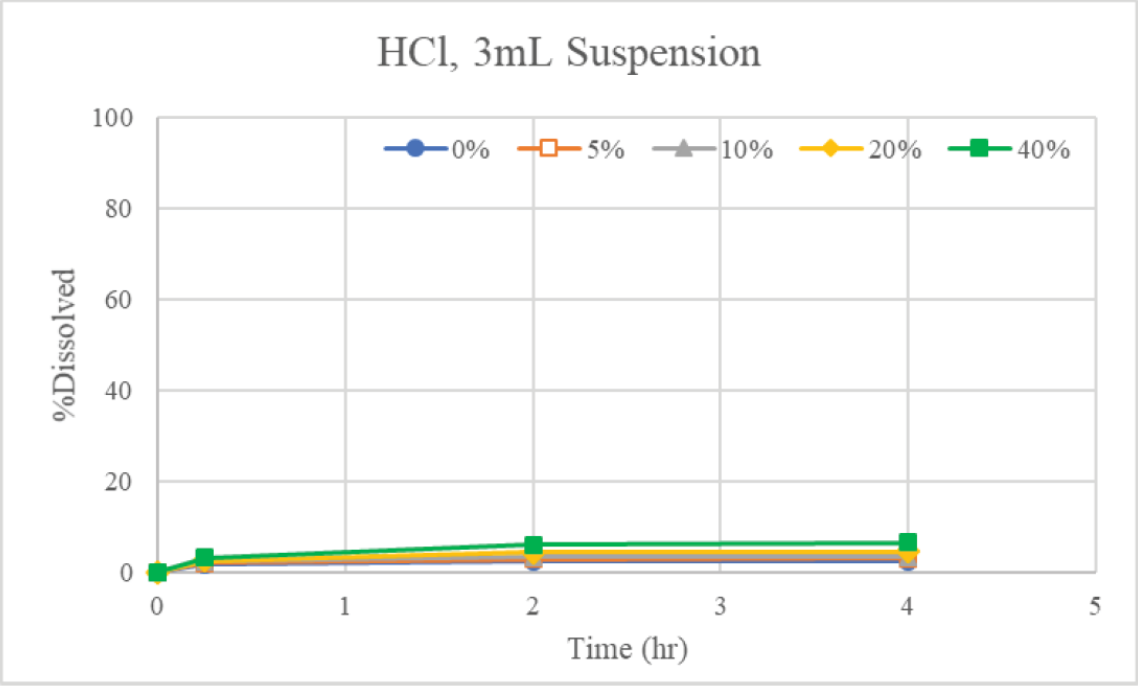
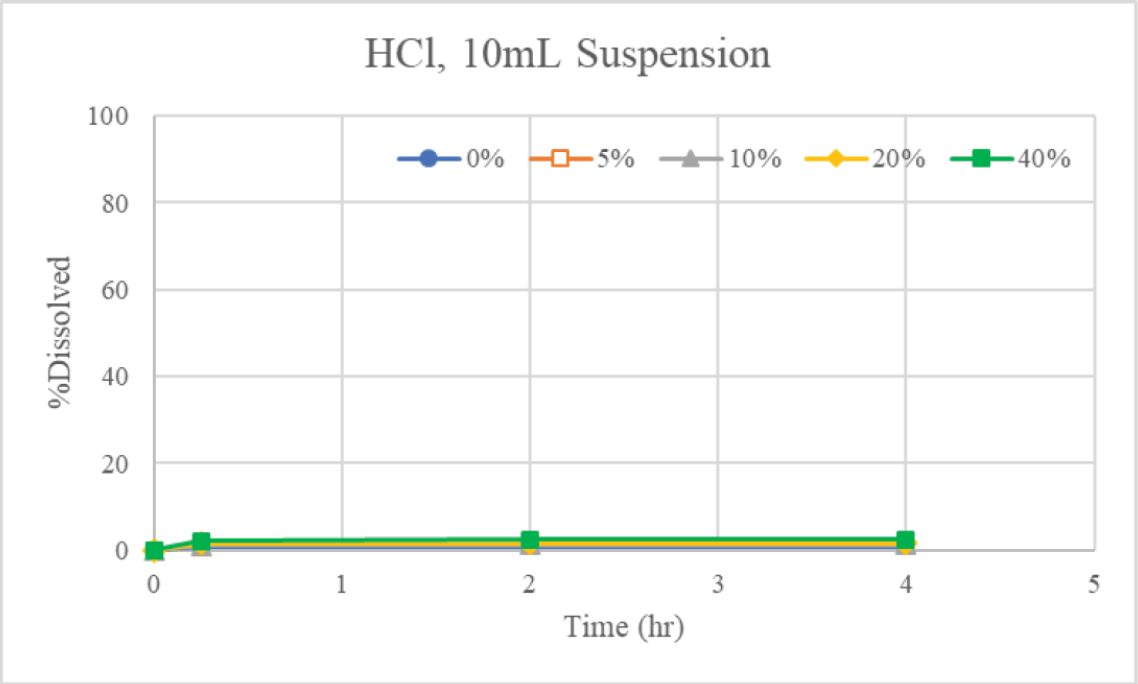


Figure 2 Dissolution Plots (0.1 mol/L HCl, 10 mL Suspension)



Reviewer's Assessment:

There is no alcohol dose dumping effect on this product. These results were communicated to OCP reviewer.

In-Vitro Soft-food Interaction Study

Reviewer's Assessment:

There is no soft- food interaction study.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment:

Based on plasma concentration time profile seen in BE study 178-CL-208, this product is an extended release suspension.

Bridging of Formulations

Reviewer's Assessment:

The proposed drug product was used in clinical trials; hence no bridging is required.

Biowaiver Request

Reviewer's Assessment:

No biowaiver is requested.

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

No post approval commitment is needed.

Lifecycle Management Considerations

List of Deficiencies:

Primary Biopharmaceutics Reviewer Name and Date:

Assadollah Noory

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

Vidula Kolhatkar

Appendix

Clinical and registration batches

Table 11 Dissolution Data of Phase 3 Clinical Trial Material and Demonstration Batches using Proposed Dissolution Test Method (n = 6 Vessels, pH 6.8 USP Phosphate Buffer 500 mL and pH 6.8 Phosphate Buffer (Three-times (b) (4) Concentration) 500 mL, Dose: 24 mg)

Sampling Time	Phase 3 Demonstration batch†			Phase 3 Clinical batch			Mean
	Lot No. G12457E-A Initial	Lot No. G12457E-A 25°C/60%RH 33M	Lot No. G12457E-A 30°C/75%RH 33M	Lot No. 16037A[1)] Initial	Lot No. 16S0210A 25°C/60%RH 18M	Lot No. 16S0210A 30°C/75%RH 18M	
15 min.	31.5%	31.0%	29.9%	31.1%	30.6%	30.5%	30.8%
	RSD: 2.2%	RSD: 1.3%	RSD: 2.5%	RSD: 2.2%	RSD: 1.3%	RSD: 1.9%	
2 hrs.	54.8%	54.2%	52.7%	54.9%	53.7%	54.1%	54.1%
	RSD: 2.0%	RSD: 1.2%	RSD: 2.2%	RSD: 1.9%	RSD: 0.4%	RSD: 1.2%	
4 hrs.	60.7%	60.1%	58.4%	60.9%	60.0%	60.0%	60.0%
	RSD: 1.2%	RSD: 0.7%	RSD: 1.6%	RSD: 1.2%	RSD:0.4%	RSD: 0.7%	
6 hrs.	85.0%	84.2%	81.9%	85.2%	84.7%	84.0%	84.2%
	RSD: 0.5%	RSD: 0.6%	RSD: 1.2%	RSD: 0.6%	RSD: 0.3%	RSD: 0.4%	
8 hrs.	86.7%	85.8%	83.7%	86.9%	86.7%	85.9%	86.0%
	RSD: 0.5%	RSD: 0.6%	RSD: 1.3%	RSD: 0.5%	RSD: 0.5%	RSD: 0.6%	

Mean [min.% - max.%]

† Representative of the clinical (formulation C)/commercial formulation and manufacturing process

1) Packaged with the same Lot No. of bulk product as 16S0210A

Table 14 Dissolution Data of Phase 3 Clinical Trial Material and Registration Batches using Proposed Dissolution Test Method (n = 12 Vessels)

Sampling Time	Phase 3 Clinical batch		Registration batch			Mean
	Lot No. 16036A initial	Lot No. 16S0210A 25°C/60%RH 36M	Lot No. 18072G initial	Lot No. 18073H initial	Lot No. 18074G initial	
15 min.	30.5%	30.4%	31.8%	31.0%	31.5%	31.0%
	RSD: 2.3%	RSD: 1.5%	RSD: 1.1%	RSD: 2.2%	RSD: 1.0%	
2 hrs.	54.1%	53.8%	55.3%	54.1%	55.2%	54.5%
	RSD: 1.8%	RSD: 1.5%	RSD: 1.3%	RSD: 2.5%	RSD: 1.4%	
4 hrs.	60.2%	60.2%	61.7%	59.9%	61.6%	60.7%
	RSD: 1.1%	RSD: 0.9%	RSD: 1.1%	RSD:1.4%	RSD: 1.0%	
6 hrs.	84.2%	84.4%	86.0%	83.4%	86.0%	84.8%
	RSD: 0.6%	RSD: 0.5%	RSD: 0.9%	RSD: 0.7%	RSD: 0.5%	
8 hrs.	86.0%	86.0%	87.7%	85.3%	87.6%	86.5%
	RSD: 0.5%	RSD: 0.5%	RSD: 0.9%	RSD: 0.7%	RSD: 0.6%	
10 hrs.	86.4%	86.1%	88.1%	85.8%	87.9%	86.9%
	RSD: 0.5%	RSD: 0.6%	RSD: 0.9%	RSD: 0.7%	RSD: 0.5%	
24 hrs.	87.3%	87.0%	89.3%	86.4%	88.7%	87.7%
	RSD: 0.5%	RSD: 0.5%	RSD: 1.0%	RSD: 0.8%	RSD: 0.7%	

Mean [min.% - max.%]

Alcohol Dose Dumping:

Table 2 Results of Dissolution Test (0.1 mol/L HCl, 3 mL Suspension)

Alcohol Concentration (%)	%Dissolved†			f2 value‡
	15 min	2 hours	4 hours	
0	1.6 [1.6 – 1.7] SD 0.0%, RSD 0.7%	2.2 [2.2 – 2.3] SD 0.0%, RSD 2.0%	2.3 [2.2 –2.4] SD 0.1%, RSD 2.8%	-
5	1.9 [1.9 – 1.9] SD 0.0%, RSD 0.5%	2.8 [2.7 – 2.9] SD 0.0%, RSD 1.7%	2.9 [2.8 – 3.0] SD 0.1%, RSD 2.0%	97
10	2.2 [2.1 – 2.2] SD 0.0%, RSD 1.9%	3.2 [3.1 – 3.4] SD 0.1%, RSD 2.7%	3.3 [3.2 – 3.4] SD 0.1%, RSD 2.7%	94
20	2.5 [2.5 – 2.6] SD 0.0%, RSD 0.8%	4.3 [4.2 – 4.4] SD 0.1%, RSD 1.6%	4.4 [4.3 – 4.6] SD 0.1%, RSD 2.0%	84
40	3.1 [3.0 – 3.2] SD 0.1%, RSD 3.2%	5.9 [5.7 –6.1] SD 0.1%, RSD 1.9%	6.2 [6.1 – 6.3] SD 0.1%, RSD 1.5%	74

RSD: relative standard deviation

† Mean [minimum – maximum], Individual values (n = 12 vessels) are shown in the attached report.

‡ The dissolution data under 0% alcohol concentration was used as the reference.

Figure 1 Dissolution Plots (0.1 mol/L HCl, 3 mL Suspension)

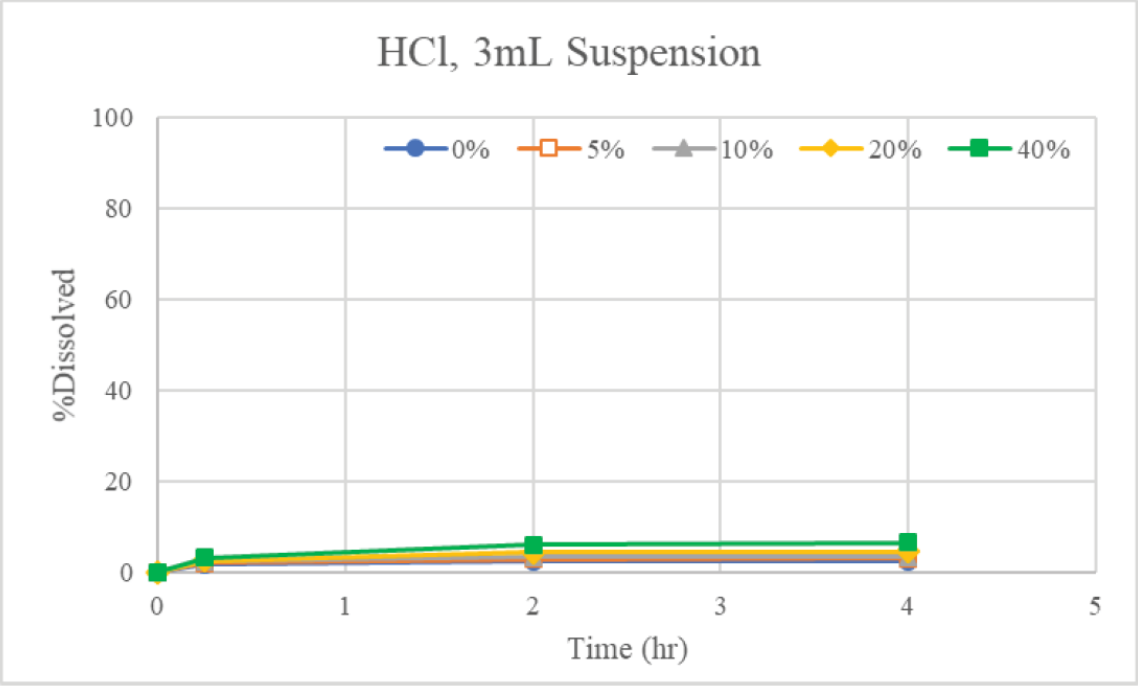


Table 3 Results of Dissolution Test (0.1 mol/L HCl, 10 mL Suspension)

Alcohol Concentration (%)	%Dissolved†			f2 value‡
	15 min	2 hours	4 hours	
0	0.8 [0.8 – 0.8] SD 0.0%, RSD 0.6%	0.9 [0.8 – 0.9] SD 0.0%, RSD 2.2%	0.9 [0.8 – 0.9] SD 0.0%, RSD 3.8%	-
5	1.0 [1.0 – 1.0] SD 0.0%, RSD 0.7%	1.0 [1.0 – 1.0] SD 0.0%, RSD 1.8%	1.0 [1.0 – 1.0] SD 0.0%, RSD 1.6%	100
10	1.1 [1.1 – 1.2] SD 0.0%, RSD 0.7%	1.2 [1.1 – 1.2] SD 0.0%, RSD 1.8%	1.2 [1.2 – 1.2] SD 0.0%, RSD 1.5%	99
20	1.5 [1.5 – 1.5] SD 0.0%, RSD 0.9%	1.6 [1.6 – 1.6] SD 0.0%, RSD 1.4%	1.6 [1.6 – 1.6] SD 0.0%, RSD 1.1%	96
40	2.1 [2.1 – 2.2] SD 0.0%, RSD 1.0%	2.5 [2.5 – 2.7] SD 0.1%, RSD 2.1%	2.5 [2.5 – 2.5] SD 0.0%, RSD 1.2%	87

RSD: relative standard deviation

† Mean [minimum – maximum], Individual values (n = 12 vessels) are shown in the attached report.

‡ The dissolution data under 0% alcohol concentration was used as the reference.

Figure 2 Dissolution Plots (0.1 mol/L HCl, 10 mL Suspension)

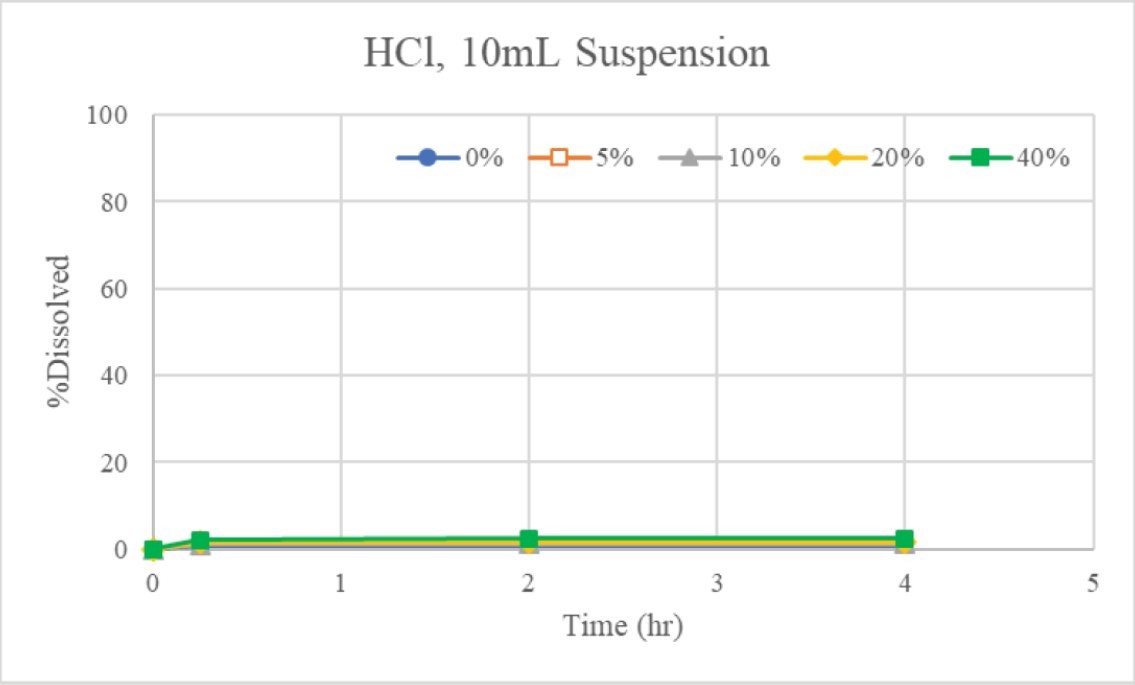


Table 4 Results of Dissolution Test (pH 6.8 Phosphate Buffer, 3 mL Suspension)

Alcohol Concentration (%)	%Dissolved†					f2 value up to 4 hours‡
	15 min	2 hours	4 hours	6 hours	8 hours	
0	31.0 [29.7 – 31.9] SD 0.7%, RSD 2.2%	54.1 [51.3 – 55.9] SD 1.3%, RSD 2.5%	59.9 [58.6 – 61.4] SD 0.8%, RSD 1.4%	83.4 [82.5 – 84.6] SD 0.6%, RSD 0.7%	85.3 [84.3 – 86.4] SD 0.6%, RSD 0.7%	-
5	39.5 [39.2 – 40.0] SD 0.2%, RSD 0.5%	67.2 [66.2 – 68.2] SD 0.5%, RSD 0.7%	74.0 [73.0 – 74.7] SD 0.4%, RSD 0.5%	93.7 [92.8 – 95.4] SD 0.7%, RSD 0.8%	94.3 [93.2 – 95.0] SD 0.6%, RSD 0.6%	46
10	46.7 [45.7 – 48.4] SD 0.8%, RSD 1.7%	76.7 [75.6 – 78.4] SD 0.9%, RSD 1.1%	82.4 [81.3 – 83.6] SD 0.7%, RSD 0.9%	96.6 [95.0 – 98.1] SD 0.8%, RSD 0.8%	96.4 [95.4 – 97.4] SD 0.5%, RSD 0.5%	34
20	57.6 [56.0 – 58.8] SD 0.9%, RSD 1.5%	88.9 [87.4 – 90.1] SD 0.9%, RSD 1.0%	92.9 [91.3 – 94.3] SD 1.2%, RSD 1.3%	100.8 [98.8 – 102.6] SD 1.4%, RSD 1.4%	99.9 [97.9 – 101.8] SD 1.6%, RSD 1.6%	25
40	70.4 [68.3 – 71.6] SD 1.0%, RSD 1.4%	98.0 [95.1 – 99.9] SD 1.4%, RSD 1.4%	100.5 [97.9 – 102.2] SD 1.4%, RSD 1.4%	105.2 [103.0 – 107.9] SD 1.4%, RSD 1.3%	102.6 [100.2 – 104.7] SD 1.4%, RSD 1.4%	19

RSD: relative standard deviation

† Mean [minimum – maximum], Individual values (n = 12 vessels) are shown in the attached report.

‡ The dissolution data under 0% alcohol concentration was used as the reference.

Figure 3 Dissolution Plots (pH 6.8 Phosphate Buffer, 3 mL Suspension)

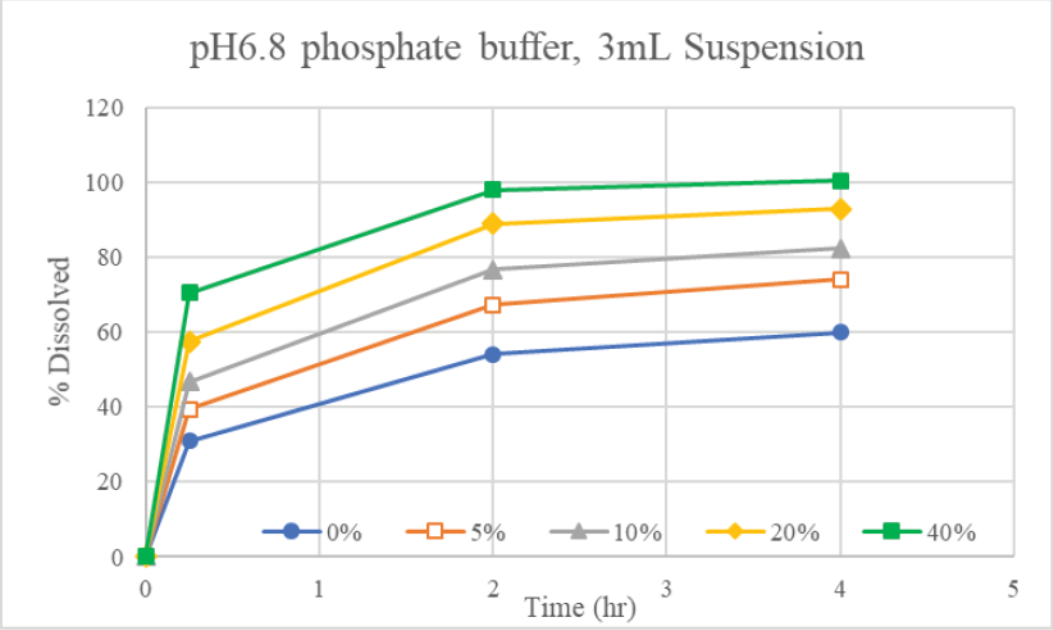


Table 5 Results of Dissolution Test (pH 6.8 Phosphate Buffer, 10 mL Suspension)

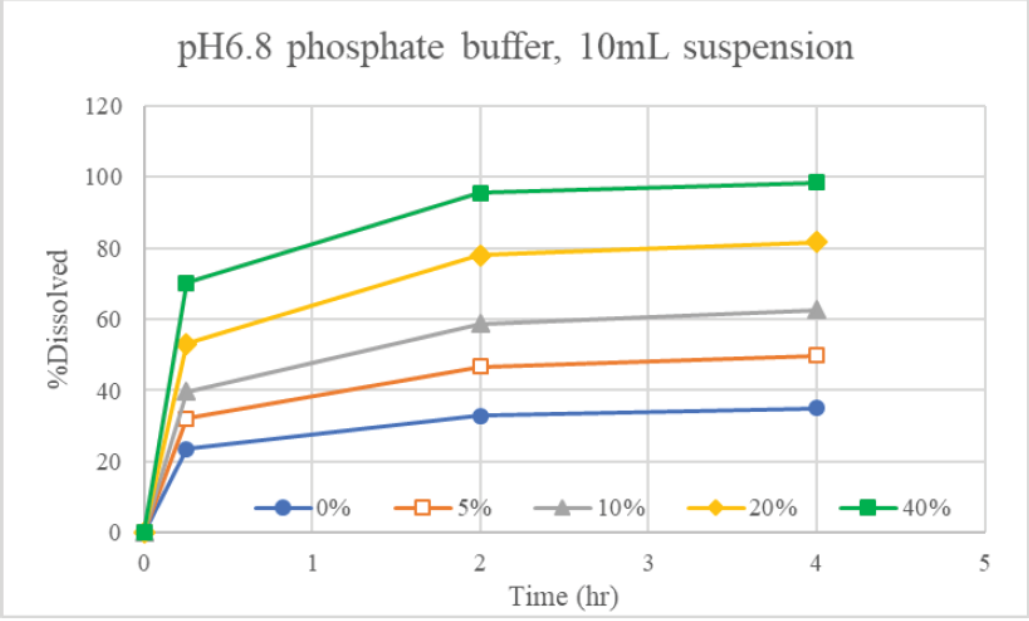
Alcohol Concentration (%)	%Dissolved†					f2 value up to 4 hours‡
	15 min	2 hours	4 hours	6 hours	8 hours	
0	23.6 [23.2 – 24.1] SD 0.3%, RSD 1.3%	32.9 [32.5 – 33.3] SD 0.3%, RSD 0.9%	35.1 [34.8 – 35.5] SD 0.2%, RSD 0.5%	69.7 [69.1 – 70.7] SD 0.5%, RSD 0.8%	72.8 [72.2 – 73.5] SD 0.4%, RSD 0.6%	-
5	32.1 [31.6 – 32.5] SD 0.3%, RSD 0.9%	46.7 [46.1 – 47.2] SD 0.3%, RSD 0.7%	49.9 [49.4 – 50.5] SD 0.3%, RSD 0.6%	81.0 [80.5 – 81.7] SD 0.4%, RSD 0.5%	82.8 [82.3 – 83.6] SD 0.4%, RSD 0.5%	45
10	39.6 [39.0 – 40.4] SD 0.4%, RSD 1.1%	58.7 [57.9 – 59.5] SD 0.5%, RSD 0.8%	62.6 [61.9 – 63.4] SD 0.4%, RSD 0.7%	88.2 [87.5 – 89.0] SD 0.5%, RSD 0.5%	88.7 [88.2 – 89.9] SD 0.5%, RSD 0.5%	31
20	53.1 [52.3 – 54.0] SD 0.7%, RSD 1.3%	78.0 [76.9 – 79.4] SD 0.9%, RSD 1.1%	81.7 [80.1 – 83.5] SD 1.0%, RSD 1.2%	97.0 [95.0 – 99.3] SD 1.3%, RSD 1.3%	96.3 [94.0 – 98.2] SD 1.3%, RSD 1.4%	19
40	70.2 [68.7 – 71.9] SD 1.1%, RSD 1.5%	95.6 [93.9 – 97.4] SD 1.2%, RSD 1.3%	98.4 [96.9 – 100.4] SD 1.2%, RSD 1.2%	104.6 [101.9 – 107.7] SD 1.6%, RSD 1.5%	102.9 [100.8 –106.5] SD 1.6%, RSD 1.6%	12

RSD: relative standard deviation

† Mean [minimum – maximum], Individual values (n = 12 vessels) are shown in the attached report.

‡ The dissolution data under 0% alcohol concentration was used as the reference.

Figure 4 Dissolution Plots (pH 6.8 Phosphate Buffer, 10 mL Suspension)



Assadollah Noory

Digitally signed by Assadollah Noory
Date: 3/15/2021 10:13:06AM
GUID: 508da6e000026b551cdd0c6e5c90e9f3

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 3/15/2021 10:17:05AM
GUID: 5424aeae00c3274f93e50573f7ca407e

CHAPTER VII: MICROBIOLOGY

Product Information	Non-sterile, non-aqueous, (b) (4) granules
NDA Number	213801
Assessment Cycle Number	1
Drug Product Name/ Strength	Mirabegron / 25 mg, 50 mg
Route of Administration	Oral
Applicant Name	Astellas Pharma Global Development, Inc
Manufacturing Site	Astellas Pharma Tech Co., Ltd. 180 Ozumi Yaiqu-shi, Shizuoka, Japan 425-0072
Method of Sterilization	N/A (drug product is non-sterile)

Assessment Recommendation: **Adequate**

Assessment Summary: This review covers the microbiological quality of the (b) (4) non-sterile, non-aqueous drug product. The applicant's response to the information request (IR) was adequate.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD 0001	**9/28/2020**
eCTD 0006	**12/11/2020**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is manufactured as non-sterile, non-aqueous, (b) (4) granules, which are then reconstituted with water as a suspension in the primary container closure system at the time of dispensing by the pharmacist.

An IR was issued by the Agency, dated 12/1/2020. The applicant's response was received 12/11/2020 and is addressed in the appropriate section of this review.

Concise Description of Outstanding Issues: None

Supporting Documents: None

S DRUG SUBSTANCE

N/A. Drug substance is supplied non-sterile.

Assessment: *Adequate*

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Yellowish-white granules.

- **Drug product composition –**

Table 1: Composition of Mirabegron granules for oral suspension

Component	Function	Reference to Standard	Quantity (mg)	Quantity (mg/bottle)
Mirabegron	Active ingredient	in house	100	830
Sodium polystyrene sulfonate	(b) (4)	USP, Ph. Eur.		(b) (4)
Diluted hydrochloric acid		NF, Ph. Eur.		
Xanthan gum		NF, Ph. Eur.		
Mannitol		USP, Ph. Eur.		
Acesulfame potassium		NF, Ph. Eur.		
Methylparaben		NF, Ph. Eur.		
Ethylparaben		NF, Ph. Eur.		
Simethicone		USP, Ph. Eur.		
Hypromellose		USP, Ph. Eur.		
Magnesium stearate		NF, Ph. Eur.		
Silicon dioxide		NF, Ph. Eur.		
Total		-	1000	8300 ‡

Table 1 was reproduced from Table 1 in "3.2.P.1 Description and Composition," located in in Module 3.2.P.1

- **Description of container closure system** –
  - Primary: 4 oz (b) (4) bottle with 24 mm child-resistant cap and (b) (4) seal
  - Secondary: Aluminum pouch with desiccant

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Jason God

Digitally signed by Jason God
Date: 12/17/2020 01:21:15PM
GUID: 56e1bae0001680fc58a5ce226a4481ab

Julie Nemecek

Digitally signed by Julie Nemecek
Date: 12/17/2020 01:24:22PM
GUID: 5277e82100088e39e79f3393e72134cf

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HONG CAI
03/24/2021 04:58:09 PM