CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213674Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 213674
Review #1

Drug Name/Dosage Form	Xtandi® enzalutamide Tablets
Strength	40 mg and 80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Astellas Pharma Us Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	10/30/2019	API/DP/Process/Facility/Biopharm
Quality Amendment 0002	11/26/2019	API/DP/Process/Facility/Biopharm
Quality Amendment 0003	12/05/2019	DP (Trade name)
Quality Amendment 0004	12/01/2019	API/DP/Process/Facility/Biopharm
Quality Amendment 0005	12/20/2019	DP (Labeling)
Quality Amendment 0006	01/09/2020	DP (Labeling)
Quality Amendment 0008	04/10/2020	API/DP/Process/Facility/Biopharm
Quality Amendment 0009	04/29/2020	DP (Labeling)
Quality Amendment 0010	05/07/2020	API/DP/Process/Facility/Biopharm
Quality Amendment 0011	05/19/2020	DP (Labeling)
Quality Amendment 0012	06/02/2020	API/DP/Process/Facility/Biopharm

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Mohd Shahjahan Kabir	Ali Al Hakim
Drug Product	William Adams	Anamitro Banerjee
Process/Facility	Lixia Cai	Daniel Obrzut
Microbiology	N/A	
Biopharmaceutics	Mei Ou	Banu S. Zolnik
Regulatory Business	Kristine Leahy	

Process Manager		
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	William Adams	Anamitro Banerjee

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	06/02/2020	No review is needed since adequate information provided in NDA.
	Type III			Adequate	06/02/2020	No review is needed since adequate information provided in NDA.
	Type III			Adequate	06/02/2020	No review is needed since adequate information provided in NDA.
	Type III			Adequate	06/02/2020	No review is needed since adequate information provided in NDA.
	Type III			Adequate	06/02/2020	No review is needed since adequate information provided in NDA.
	Type III			Adequate	06/02/2020	No review is needed since adequate information provided in NDA.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA submission and reviews	NDA 203415	The applicant's own NDA with the capsule formulation

2. CONSULTS

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

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Product quality review team recommends Approval of NDA 213674 based on the adequate CMC information submitted in the NDA and acceptable facilities status.

II. Summary of Quality Assessments

A. Product Overview

Enzalutamide capsule (NDA 203415) was first approved in the US in Aug 2012 under the trade name Xtandi® for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel. The applicant of the NDA, Astellas, submits this 505b1 NDA to seek approval of Xtandi Enzalutamide tablets for the same indication as the marketed Xtandi® capsules. The approved enzalutamide drug product is an immediate-release liquid-filled soft capsule containing 40 mg of enzalutamide. The recommended dose is 160 mg of enzalutamide (4 x 40 mg capsules) administered orally once daily, with or without food. Difficulty swallowing and using of multiple capsules (>4 capsules) are important issues in elderly prostate cancer patient populations and present challenges with regard to medication management, administration and adherence. To address the needs of this patient population, the applicant has developed an immediate-release 40 mg and 80 mg tablet dosage form of enzalutamide. The application is based on the results of a pivotal clinical study to demonstrate bioequivalence between Enzalutamide Capsules and Tablets for single-dose AUC under fasted and fed conditions. The drug substance is sourced from the same supplier as that for NDA #203415. (b) (4)

Proposed Indication(s) including Intended Patient Population	XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with: • castration-resistant prostate cancer. • metastatic castration-sensitive prostate cancer.
Duration of Treatment	Until disease progression
Maximum Daily Dose	XTANDI 160 mg (two 80 mg tablets or four 40 mg tablets or four 40 mg capsules) administered orally once daily.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The following is a summary of key assessments from the reviews of drug substance, drug product, manufacturing and facility, and biopharmaceutics found in the respective technical chapters for each discipline. A summary of the assessments is provided in this section. Section D further discusses key review issues in greater detail.

Drug Substance: **Adequate**

The NDA 213674 applicant cross-referenced the FDA approved NDA 203415 for CMC information on the drug substance, enzalutamide. Enzalutamide specification is the same as in the cross-referenced approved NDA 203415. Batch analyses data contained in the submission conformed to the proposed enzalutamide specification. The proposed retest period for enzalutamide is (b) (4) based on stability data referred to the approved NDA 203415. Refer to the FDA approved cross-referenced NDA 213674 for all other DS-CMC information.

Drug Product: **Adequate**

The drug product is an immediate release, film-coated 40 mg and 80 mg tablets as an alternative formulation of the listed drug, Xtandi® (enzalutamide) Capsules. Enzalutamide is a BCS class 2 drug, low aqueous solubility and high intestinal permeability. (b) (4)

(b) (4)

Drug substance is obtained from (b) (4)

. Tablets for use in the US are manufactured and controlled at Pfizer Pharmaceuticals LLC (Puerto Rico). Drug substance meets the supplier's specification for identity, assay, purity and physicochemical attributes. Excipients in the (b) (4) and tablet core are USP/NF grade. No excipient is novel, or of animal or human origin.

The proposed specification for release and stability addresses appearance, identity (HPLC), assay (HPLC), degradants (HPLC), dissolution (HPLC), physical form (b) (4) and microbial limits (USP). The proposed analytical methods are described in sufficient detail and validated for appropriate attributes. The proposed criteria are justified based on ICH Q3B, manufacturing experience and the submitted stability study results. All tablet batches met the specification in use at time of testing.

The commercial presentation is a 75cc high density polyethylene bottle with child resistant closure and heat induction innerseal. Bottle fill is 60-count (prescription) and 28-count (physical sample) for 80 mg tablets; and 120-count (prescription) and 56-count (physical sample) for 40 mg tablets.

The stability studies consist of primary studies, supportive studies, heat/humidity stress studies, a tablet photostability study, (b) (4), and a bulk tablet hold study. (b) (4). The studies were found to be acceptable for their intended purpose. The stress and photostability studies show that tablets are not sensitive to humidity or light. (b) (4)

Based on the stability data, the proposed 48-month expiration dating period for the drug stored at 20-25ºC is deemed acceptable.

Pharmaceutical Manufacturing and Facility: **Adequate**

(b) (4)

All drug substance and drug product manufacturing and testing are deemed acceptable based on Pre-Approval Inspection results and inspection history for multiple facilities.

Biopharmaceutics: **Adequate**

The drug substance, enzalutamide, is a BCS II compound. The proposed Enzalutamide Tablets are supplied with two strengths, 40 mg and 80 mg. The proposed dose is 160 mg (two 80 mg tablets or four 40 mg tablets) administered orally once daily.

Five in vivo relative bioavailability/bioequivalence (BA/BE) studies, including four pilot BA studies (MDV3100-05, 9785-CL-0010, MDV3100-19, and 9785-CL-0003) using development formulations (Tablets A, B, C, E and F), and one pivotal BE study (9785-CL-0014) using to-be-marketed (TBM) formulation (2 x 80 mg tablets) compared to the approved product (4 x 40 mg capsules), were conducted to support the current NDA 213674 submission. The study 9785-CL-0014 is the pivotal in vivo BA/BE study to support the approval of this NDA. This study has been reviewed and accepted by the Office of Clinical Pharmacology (OCP), per OND mid-cycle meeting

held on 03/17/2020.

The Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Enzalutamide Tablets, 40 mg and 80 mg; (ii) the in vitro formulation bridging studies between the clinical and the commercial formulations and batches; (iii) biowaiver for the lower strength (40 mg) of Enzalutamide Tablets.

In Vitro Dissolution Testing of the Finished Product:
The dissolution method parameters have been evaluated and found acceptable. The proposed dissolution method showed acceptable discriminating ability with regards to different clinical formulations, (b) (4), and formulation variations. Therefore, the proposed dissolution method is **acceptable** as a quality control (QC) test for the proposed drug product for batch release and stability testing. The overall dissolution data support the proposed acceptance criterion of Q= (b) (4)% in 30 minutes.

The final approved in vitro dissolution method and acceptance criterion for the proposed Enzalutamide Tablets, 40 mg and 80 mg, are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium	900 mL of phosphate buffer, pH 7.5
Temperature	37°C±0.5°C
Acceptance Criterion	Q= (b) (4)% in 30 minutes

The In Vitro Formulation Bridging:
The pharmacokinetics (PK) parameters of the five formulations during development (Tablets A, B, C, E and F) accepted by OCP. No additional in vitro studies are needed for bridging the five development formulations.

The pivotal BE formulation (Tablet E) Therefore, the biowaiver request of the proposed lower strength product, Enzalutamide Tablets, 40 mg, is granted per 21 CFR 320.22(d)(2).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Final Risk Assessments

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	L	The assay shows little change on stability. No trends observed.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		L	(b) (4)
Content uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		L	DP manufacturing process studies showed content uniformity is in control.
(b) (4)		M		L	(b) (4)
Microbial limits	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		L	Testing performed at release and stability
Dissolution – BCS Class II & IV	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		L	Method has discriminating ability with regards to different clinical formulations, (b) (4) form, and formulation variations.

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
13-Jul-2020

Xiao Chen

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LABELING

(as submitted in amendment SN-011 dated 05/19/20)

R Regional Information

1.14 Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XTANDI® safely and effectively. See full prescribing information for XTANDI.
XTANDI® (enzalutamide) capsules, for oral use
XTANDI® (enzalutamide) tablets, for oral use

DOSAGE FORMS AND STRENGTHS
Capsule: 40 mg (3)
Tablet: 40 mg, 80 mg (3)

FULL PRESCRIBING INFORMATION
3 DOSAGE FORMS AND STRENGTHS
XTANDI 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ.
XTANDI 40 mg tablets are yellow, round, film-coated and debossed with E 40.
XTANDI 80 mg tablets are yellow, oval, film-coated and debossed with E 80.

11 DESCRIPTION
Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide.

The molecular weight is 464.44 and molecular formula is C21H16F4N4O2S. The structural formula is:
[molecular structure]
Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

XTANDI is available as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

XTANDI is also available as film-coated tablets for oral administration. Each tablet contains 40 mg or 80 mg of enzalutamide. The inactive ingredients are hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate. The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ and are available in the following package size:

- Bottles of 120 capsules with child resistant closures (NDC 0469-0125-99)

XTANDI (enzalutamide) 40 mg tablets are supplied as yellow, round, film-coated tablets debossed with E 40, and are available in the following package size:

- Bottles of 120 tablets with child resistant closures (NDC 0469-0625-99)

XTANDI (enzalutamide) 80 mg tablets are supplied as yellow, oval, film-coated tablets debossed with E 80, and are available in the following package size:

- Bottles of 60 tablets with child resistant closures (NDC 0469-0725-60)

Recommended storage: Store XTANDI capsules and tablets at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

Swallow capsules or tablets whole. Do not chew, dissolve or open the capsules. Do not cut, crush, or chew the tablets.

17 PATIENT COUNSELING INFORMATION

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017
234833-XTA-USA

Rx Only

XTANDI® is a registered trademark of Astellas Pharma Inc.

PATIENT INFORMATION

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules and tablets dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

What are the ingredients in XTANDI?

XTANDI Capsules
Active ingredient: enzalutamide
Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide

XTANDI Tablets

Active ingredient: enzalutamide
Inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.
The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062
Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017
234833-XTA-USA

XTANDI® is a registered trademark of Astellas Pharma Inc. For more information go to www.Xtandi.com or call 1-800-727-7003.

Reviewer's Assessment: Acceptable

Highlights of Prescribing Information

Product Name: Established and trade names for each dosage form is acceptable.
Dosage Forms and Strengths: CMC information is complete and correct.

Full Prescribing Information

Section 3: Dosage form descriptions are correct.
Section 11: CMC information, including formulation statements, is complete and correct.
Section 16: The commercial presentations are complete and correct; noted that eh physician samples are not included. Storage at USP controlled room temperature is supported by the studies in module 3.2.P.8. The "Swallow capsule or tablets whole…" statement is accepted from the capsule package insert.
Section 17: "Manufactured by" and 'Marketed by" statements are acceptable. "234833-XTA-USA" is an Astellas marketing code, thus acceptable. "Rx only" and trademark statements are acceptable.

Patient Information

Formulation statements are complete and correlate to the Full Prescribing Information section. "Manufactured by" and 'Marketed by" statements are acceptable. "234833-XTA-USA" is an Astellas marketing code, thus acceptable. "Rx only" and trademark statements are acceptable .

Immediate Container Label

(b) (4)

Reviewer's Assessment: Acceptable

40 mg and 80 mg tablet bottle labels are the same, except for NDC, strength identity and tablet count. Information is complete and supported by the NDA studies. The controlled room temperature storage statement is supported by module 3.2.P.8. The "do not chew," and "manufactured by" statements are taken from the package insert for capsules. The commercial presentation for 40 mg strength is a 120-count bottle and for 80 mg strength is a 60-count bottle. CMC information matches that on the carton label.

Carton Labeling

(b) (4)

Reviewer's Assessment: Acceptable

40 mg and 80 mg tablet carton labels are the same, except for NDC, strength identity and tablet count. Information is complete and supported by the NDA studies. The controlled room temperature storage statement is supported by module 3.2.P.8. The "do not chew," and "manufactured by" statements are taken from the package insert for capsules. The commercial presentation for 40 mg strength is a 120-count bottle and for 80 mg strength is a 60-count bottle. CMC information matches that on the bottle label.

List of Deficiencies: None

Primary Labeling Reviewer: *William Adams, 06/02/20*

Secondary Reviewer: Anamitro Banerjee, 06/02/20

William Adams

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 213674 [505(b)(1)]
Drug Product Name/Strength: XTANDI® (Enzalutamide) Tablets 40 mg and 80 mg
Route of Administration: Oral
Proposed Indication: For the treatment of patients with castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer
Applicant Name: Astellas Pharma US, Inc.
Submission Date: 10/30/2019
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

EXECUTIVE SUMMARY

Enzalutamide is an androgen receptor (AR) inhibitor that targets the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs and consequently inhibits nuclear translocation of the AR and inhibits the association of the AR with DNA even in the setting of AR overexpression, as well as in prostate cancer cells resistant to antiandrogens such as bicalutamide.

There is an approved enzalutamide drug product, XTANDI® (Enzalutamide) **Capsules**, 40 mg, by Astellas Pharma US. XTANDI capsule is an immediate-release liquid-filled soft capsule (approved under NDA 203415 on 08/31/2012). The recommended dose is 160 mg of enzalutamide (4 x 40 mg capsules) administered orally once daily, with or without food, with the possibility of dose reduction to 80 mg or 120 mg should toxicity or intolerable side effects occur.

The same Applicant (Astellas Pharma US) submitted the current NDA 213674, a 505(b)(1) application, to seek the approval of the proposed XTANDI® (Enzalutamide) **Tablets,** 40 mg and 80 mg, which are the immediate-release tablets with a (b) (4) colored film-coating to address the needs of patient population by reducing the number of dosage units from 4 x 40 mg capsules to 2 x 80 mg tablets. The Applicant stated that the introducing of the 40 mg tablet strength will facilitate patient adherence to the prescribed dose while allowing for dose reduction to 120 mg with the 40 mg tablets. The proposed drug product has the same indication for the treatment of patients with castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer.

The drug substance (DS), enzalutamide, is a BCS II compound. The drug product (b) (4)

Enzalutamide Tablets, the immediate release film-coated tablets.

The proposed Enzalutamide Tablets are supplied with two strengths, 40 mg and 80 mg. The proposed dose is 160 mg (two 80 mg tablets or four 40 mg tablets) administered orally once daily.

Five in vivo relative bioavailability/bioequivalence (BA/BE) studies, including four pilot BA studies (MDV3100-05, 9785-CL-0010, MDV3100-19, and 9785-CL-0003) using development formulations (Tablets A, B, C, E and F), and one pivotal BE study (9785-CL-0014) using to-be-marketed (TBM) formulation (2 x 80 mg tablets) compared to the approved product (4 x 40 mg capsules), were conducted to support the current NDA 213674 submission. The study 9785-CL-0014 is the pivotal in vivo BA/BE study to support the approval of this NDA. This study has been reviewed and accepted by the Office of Clinical Pharmacology (OCP), per OND mid-cycle meeting held on 03/17/2020.

The Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Enzalutamide Tablets, 40 mg and 80 mg; (ii) the in vitro formulation bridging studies between the clinical and the commercial formulations and batches; (iii) biowaiver for the lower strength (40 mg) of Enzalutamide Tablets.

In Vitro Dissolution Testing of the Finished Product:
The dissolution method parameters have been evaluated and found acceptable. The proposed dissolution method showed acceptable discriminating ability with regards to different clinical formulations, (b) (4), and formulation variations. Therefore, the proposed dissolution method is **acceptable** as a quality control (QC) test for the proposed drug product for batch release and stability testing. The overall dissolution data support the proposed acceptance criterion of Q (b) (4)% in 30 minutes.

The final approved in vitro dissolution method and acceptance criterion for the proposed Enzalutamide Tablets, 40 mg and 80 mg, are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium	900 mL of phosphate buffer, pH 7.5
Temperature	37ºC±0.5ºC
Acceptance Criterion	Q (b) (4)% in 30 minutes

The In Vitro Formulation Bridging:
The pharmacokinetics (PK) parameters of the five formulations during development (Tablets A, B, C, E and F) accepted by OCP. No additional in vitro studies are needed for bridging the five development formulations.

The pivotal BE formulation (Tablet E) Therefore, the biowaiver request of the proposed lower strength product, Enzalutamide Tablets, 40 mg, is granted per 21 CFR 320.22(d)(2).

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 213674 for the proposed drug product, XTANDI® (Enzalutamide) Tablets, 40 mg and 80 mg, is recommended for **APPROVAL.**

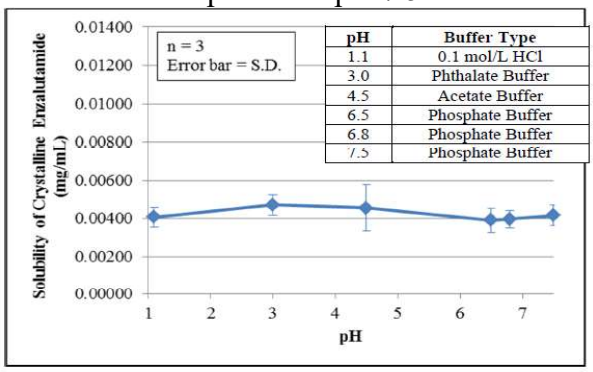
BIOPHARMACEUTICS REVIEW

1. Drug substance solubility and permeability

According to the Applicant, the crystalline enzalutamide (b) (4) has low aqueous solubility (<3.0 µg/mL in pH 1.0 to pH 11.0 aqueous buffers and in water, *data from M.3.2.S.3.1 of NDA 203415*) and high permeability across Caco-2 monolayers [with apparent permeability coefficient from apical to basal ($P_{app\ A->B}$) $\geqslant$ 31 x 10^{-6} cm/sec, which is more than twice of high permeability reference compound propranolol (P_{app} = 14.8 x 10^{-6} cm/sec), and more than ten times of low permeability reference compound mannitol (P_{app} = 0.273 x 10^{-6} cm/sec), *data from M.5.3.2.3 of NDA 203415, study 9785-me-0031, in vitro permeation study of MDV3100 across a monolayer of cultured Caco-2 cells*].

As the data presented in the following Figures 1 and 2 (*data from the current NDA*), crystalline enzalutamide has low solubility (with approximately 0.004 mg/mL in aqueous buffers), (b) (4) The pH 7.5 medium was further evaluated for its suitability as dissolution medium and discriminating ability, (b) (4)

Figure 1: Solubility of crystalline enzalutamide in 100 mL of media at pH 1.1 to pH 7.5



HCl, hydrochloric acid; S.D., standard deviation

(b) (4)

(b) (4)

Therefore, this Reviewer considers that due to (b) (4) , the risk of product failure for the final drug product (b) (4) has been mitigated.

2. In vitro dissolution method development

Dissolution is one of the critical quality attributes (CQAs) of the proposed drug product. FDA's requirements regarding the dissolution method development were conveyed to the Applicant in the cross-referenced IND 74563, a Type C meeting minutes, on 11/10/2014. The dissolution method development was submitted under the same IND, in a Type C meeting package, on 07/01/2015. FDA's comments regarding the dissolution method development and the discriminating ability were conveyed in the WRO for this Type C meeting request on 07/22/2015. The dissolution method development is summarized in M.3.2.P.5.6 in current NDA submission.

Per the Applicant, the proposed 80 mg tablets were used for method development, while the 40 mg tablets were used to confirm the developed dissolution method. The proposed dissolution method and acceptance criterion are listed as below.

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium	900 mL of phosphate buffer, pH 7.5
Temperature	37°C±0.5°C
Sampling Time	15, 20, and 30 minutes
Acceptance Criterion	Q= (b) (4)% in 30 minutes

The following parameters have been evaluated for determining the dissolution method, summarized as:

(b) (4)

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(b) (4)

(3) Discriminating ability:

(a) Discrimination to differing clinical formulations: There are five development formulations used in clinical studies, including Tablet A, B, C, E, F and to-be-marked (TBM) formulation. (b) (4) The development and commercial formulations and related clinical studies are presented in Table 1.

Table 1: Composition of Tablets evaluated in clinical studies

Component	Tablet A (160 mg)	Tablet B (80 mg)	Tablet C (80 mg)	Tablet E (80 mg)	Tablet F (80 mg)	TBM Tablet (80 mg)
Study: Lot # used in clinic (manufacturing site)	MDV3100-05: FPH-10-016 (b) (4) 9785-CL-0003: FPH-12-010a (b) (4)	9785-CL-0010: #12075A (ATEC)	9785-CL-0010: #12074A (ATEC)	MDV3100-19: FPH14-030a (b) (4)	MDV3100-19: FPH14-029a (b) (4)	9785-CL-0014: PMGY/ SBGX (b) (4)
(b) (4)						
Core Tablet Composition (mg):						
Enzalutamide (b) (4)						
(b) (4)						
Microcrystalline cellulose (b) (4)						
Croscarmellose sodium (b) (4)						
Colloidal silicon dioxide						
Magnesium stearate						
Total core tablet weight (mg)						
Total coated tablet weight (mg)						**669.5 (yellow)**

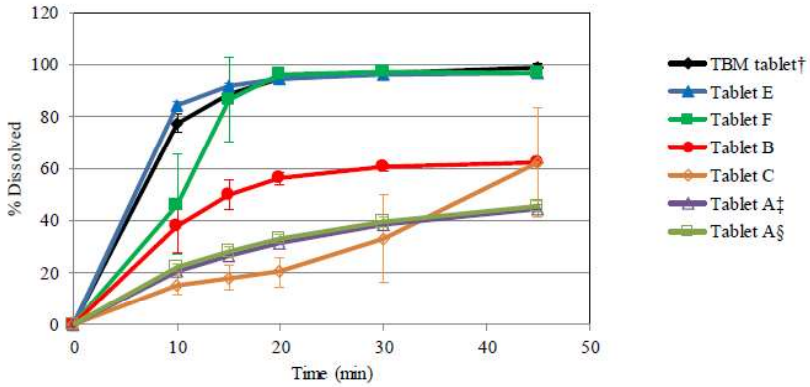
ATEC: Astellas Pharma Tech Co. Ltd.; HPMCAS: Hypromellose acetate succinate; PMGY: bulk tablet lot; SBGX: packaged lot number; (b) (4) TBM: to-be-marketed

(b) (4)

Source: [Module 3.2.P.2.2, Table 29 and Table 30]

The composition of Tablet E is identical to the proposed commercial TBM tablet, and lot # PMGY (same composition represents Tablet E and TBM tablet, per the Applicant) was used in the pivotal BE study (9785-CL-0014). As the dissolution profiles presented in Figure 7 below, TBM tablet and Tablet E have comparable dissolution. The slower dissolution of Tablet F at 10 minutes (b) (4) as compared to the TBM as well as Tablet E tablets. All other formulations (Tablets A, B, and C) had different dissolution profiles compared to TBM and Tablet E tablets.

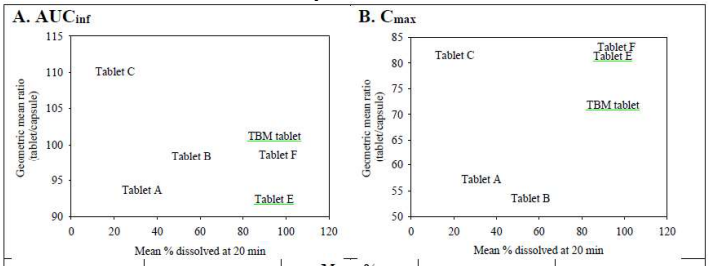
Figure 7: Dissolution profiles of different clinical and TBM formulations (n=6)



Mean (SD) values are plotted. Dissolution was tested at pH 7.5 per the method proposed for routine quality control of 80 and 40 mg tablets. All tablets shown in the plot were 80 mg strength except for Tablet A, which was 160 mg strength. To enable a direct comparison of the dissolution profiles, the Tablet A tablets were cut in half prior to the dissolution testing. TBM: To-be-marketed. † Lot PMGY. ‡ Lot FPH-10-016. § Lot FPH-12-010a.

However, the Applicant stated that there was no apparent relationship between the in vitro dissolution and the in vivo performance as assessed by the geometric mean ratios (GMRs) for AUC_{inf} and C_{max}. Thus, there is no evidence of correlations between the in vitro dissolution and the in vivo relative bioavailability (Table 2).

Table 2: In vitro dissolution and in vivo relative bioavailability parameters of development tablets



Tablet	Lot No.	Mean % dissolved at 20 min [range]	AUC_{inf} GMR [90% CI]	C_{max} GMR [90% CI]
Tablet A	FPH-10-016	32.8 (b) (4)	93.65 [91.18, 96.19]	57.23 [53.29, 61.46]
Tablet B	12075A	55.9	98.43 [87.43, 110.82]	53.60 [48.49, 59.24]
Tablet C	12074A	20.3	110.12 [96.44, 125.73]	81.55 [72.91, 91.23]
Tablet E	FPH-14-030a	94.4	92.44 [80.85, 105.69]	81.34 [73.29, 90.27]
Tablet F	FPH-14-029a	96.2	98.66 [85.40, 113.99]	83.19 [72.39, 95.60]
TBM tablet	PMGY	94.5	101.17 [96.77,105.77]	71.82 [66.75, 77.28]

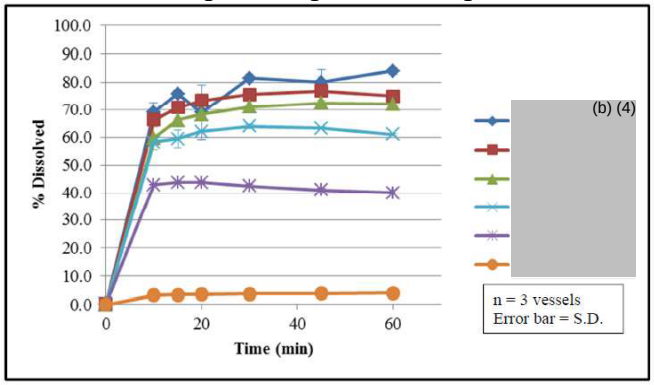
AUC_{inf} and C_{max} GMR values are based on comparisons of the tablet to capsule under fasted conditions.
CI: confidence interval; GMR: geometric mean ratio; TBM: to-be-marketed.
Source: Appendix Table 1A and statistical summary tables in Sections 2.2.1.1 and 2.2.1.3

Note that the Applicant used the word symbols of different formulations (e.g., Tablets A, B, C, E, F, and TBM tablets) in both the figures A, B and tables below the figures. A clarification IR was conveyed to the Applicant on 03/23/2020 regarding the symbols[1]. The Applicant explained the meaning of symbols in the email communication on 03/23/2020, which was acceptable. The satisfactory comments were conveyed to the Applicant in an email communication on 02/24/2020 (Appendix 1). Therefore, this Reviewer has no further questions with regards to the data/profiles showed in Table 2 above.

(b) Discrimination to (b) (4): Physical mixtures of (b) (4) enzalutamide and excipients, spiked with (b) (4) at several levels, were prepared and tested using the proposed dissolution method. As the results presented in the following Figures 8 and 9, the mixtures with the higher level ((b) (4)%) of (b) (4) showed the slower dissolution for both 40 mg and 80 mg tablets.

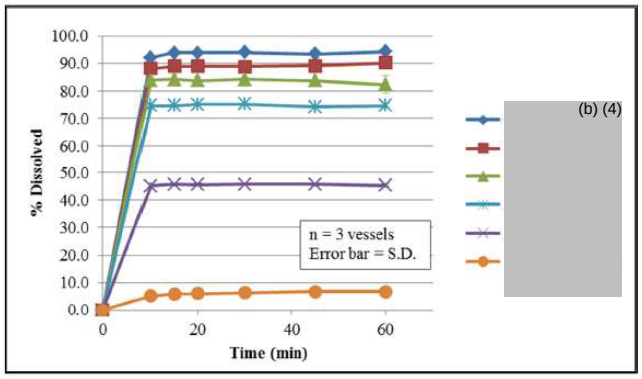
[1] https://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f883d6b8df

Figure 8: Dissolution profiles of 80 mg enzalutamide samples ([(b) (4)] spiked with [(b) (4)]) in 900 mL of pH 7.5 phosphate buffer at a paddle speed of 50 rpm



S.D., standard deviation: [(b) (4)]
Note: Error bars are not visible for several marks due to low S.D.

Figure 9: Dissolution profiles of 40 mg enzalutamide samples ([(b) (4)] spiked with [(b) (4)]) in 900 mL of pH 7.5 phosphate buffer at a paddle speed of 50 rpm



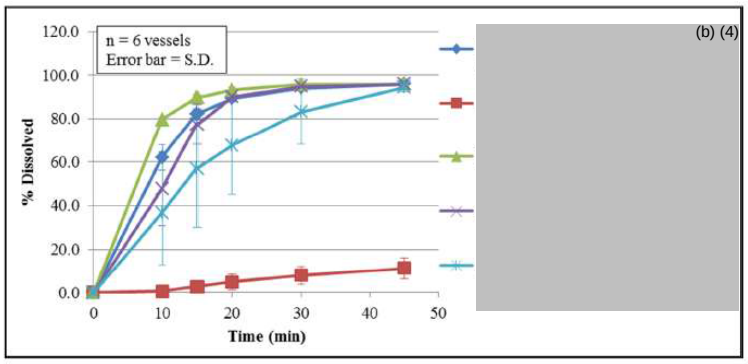
S.D., standard deviation: [(b) (4)]
Note: Error bars are not visible due to low S.D.

[(b) (4)]. Since there is no study/test to evaluate the correlation between [(b) (4)] amount and PK profiles, [(b) (4)], the risk of [(b) (4)] impacting drug performance/quality is mitigated. Additionally, [(b) (4)] is not reported being detected in the primary stability and supporting stability samples for any packaging configuration and storage condition, thus supporting the physical stability of the drug product (*data from M.3.2.P.8.3*).

(c) Discrimination to formulation variations: The Applicant intentionally manufactured tablets containing changes in either the amount of [(b) (4)] or the amount of total [(b) (4)]. The amount of the [(b) (4)] was varied from the

target (b) (4) of the core tablet) to either (b) (4) of the core tablet weight. The amount of the (b) (4) was studied at the target (b) (4) and at the higher levels of (b) (4) of the core tablet weight. As the results presented in Figure 10 below, the proposed dissolution method can discriminate the tablets with removed (b) (4) and the tablets with increased (b) (4) to 10 times-level (b) (4)

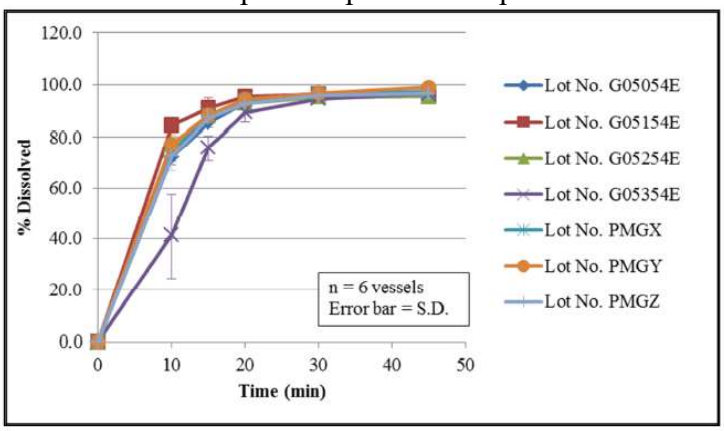
Figure 10: Dissolution profiles of Enzalutamide Tablets 80 mg containing formulation variations



S.D., standard deviation

(d) Discrimination to variations in (b) (4): The tablets generated by (b) (4), which had been manufactured with a variety of processing conditions, were used for testing. Variation of particle size and (b) (4) were generated by fluctuating (b) (4). As the results showed in the following Figure 11, all test lots showed comparable dissolution with primary stability lots (lot # PMGX, PMGY, and PMGZ) expect the slightly slower dissolution of one test lot (G05354E) at the early time-points. These results indicated that (b) (4) has minimal impacts on tablet dissolution. Therefore, the Applicant concluded that particle size and (b) (4) do not affect the CQAs of the drug product within the ranges studied.

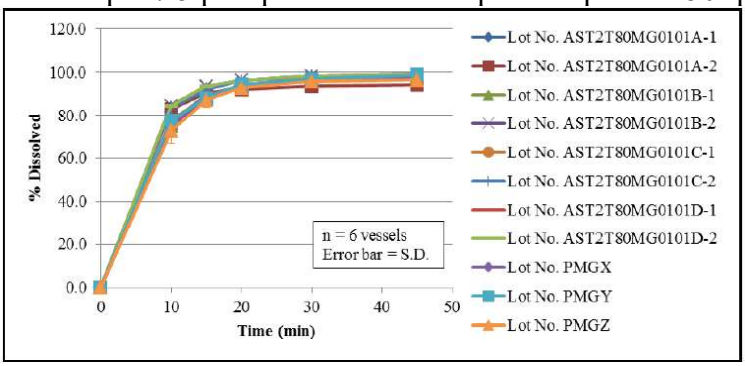
Figure 11: Dissolution profiles of Enzalutamide Tablets 80 mg prepared using (b) (4) of varying particle sizes and densities in pH 7.5 phosphate buffer at a paddle speed of 50 rpm



S.D., standard deviation

(e) Discrimination to tableting processing parameters: The Applicant also evaluate the dissolution of tablets that were manufactured using a variety of tableting process parameters (e.g., (b) (4)) for the impact on tablet hardness. From the data presented in Figure 12 below (*data from cross-referenced IND 74563 meeting package submitted on 07/01/2015*), different tablet processing parameters have little impact on tablet hardness and dissolution profiles.

Figure 12: Dissolution profiles of Enzalutamide Tablets 80 mg with variation of tableting process in pH 7.5 phosphate buffer at a paddle speed of 50 rpm



S.D.: standard deviation.

Overall, this Reviewer considers that the proposed dissolution method (USP Apparatus II Paddle, 50 rpm, 900 mL of phosphate buffer, pH 7.5) has been evaluated. The proposed dissolution method showed acceptable discriminating ability with regards to different clinical formulations, (b) (4) , and formulation variations. Therefore, the proposed dissolution method is acceptable as a quality control (QC) test for the proposed drug product.

3. Dissolution data and acceptance criterion

The dissolution data of (i) three primary stability/registration batches of Enzalutamide Tablets 80 mg [batch # PMGX, PMGY (pivotal BE batch), and PMGZ], (ii) three primary stability/registration batches of Enzalutamide Tablets 40 mg [batch # TCKD, TCKF, and TCKG], and (iii) supporting stability batches with same commercial formulations, are provided, as presented in the following Tables 3 and 4.

Table 3: Dissolution data at 15, 20 and 30 min of the Enzalutamide Tablets 80 mg (Apparatus II Paddle, 50 rpm, 900 mL of pH 7.5 phosphate buffer, n=6)

Lot No.	Data at release or long-term stability		% Dissolved, n=6 vessels, Mean [Min – Max] (RSD)		
			15 min	20 min	30 min
PMGX	Bottle	At release (T=0)	87% [(b) (4) (2.2%)	95% [(b) (4) (1.6%)	97% [(b) (4) (1.4%)
		3 months	77% [(5.2%)	87% [(2.8%)	94% [(1.6%)
		6 months	70% [(4.0%)	83% [(2.3%)	93% [(1.5%)
		9 months	85% [(1.9%)	93% [(0.9%)	97% [(0.5%)
		12 months	89% [(1.5%)	95% [(0.7%)	97% [(0.7%)
		18 months	86% [(4.2%)	92% [(2.1%)	96% [(1.4%)
		24 months	89% [(3.4%)	96% [(1.8%)	100% [(1.1%)
		36 months	81% [(3.3%)	93% [(1.9%)	97% [(1.1%)
		48 months	82% [(3.9%)	94% [(1.6%)	99% [(1.0%)
PMGY †	Bottle	At release (T=0)	82% [(3.8%)	92% [(3.7%)	96% [(1.7%)
		3 months	74% [(4.2%)	85% [(2.9%)	93% [(1.7%)
		6 months	77% [(8.4%)	86% [(1.6%)	92% [(1.8%)
		9 months	76% [(4.5%)	90% [(1.0%)	96% [(0.6%)
		12 months	90% [(1.0%)	95% [(0.5%)	98% [(0.5%)
		18 months	88% [(3.6%)	93% [(1.5%)	97% [(0.7%)
		24 months	86% [(3.3%)	95% [(0.8%)	99% [(0.8%)
		36 months	76% [(4.8%)	88% [(2.5%)	95% [(1.2%)
		48 months	82% [(4.5%)	95% [(1.3%)	99% [(0.4%)
PMGZ	Bottle	At release (T=0)	85% [(b) (4) (2.7%)	93% [(b) (4) (1.2%)	97% [(b) (4) (0.9%)
		3 months	82% [(8.7%)	92% [(2.6%)	97% [(1.0%)
		6 months	79% [(3.9%)	93% [(1.4%)	96% [(0.6%)
		9 months	73% [(4.1%)	88% [(5.0%)	94% [(0.9%)
		12 months	88% [(2.4%)	95% [(2.0%)	99% [(1.7%)
		18 months	89% [(1.5%)	95% [(0.7%)	98% [(0.7%)
		24 months	87% [(2.3%)	93% [(1.1%)	98% [(0.7%)
		36 months	86% [(1.4%)	95% [(0.9%)	102% [(b) (4) (1.1%)
		48 months	82% [(2.3%)	93% [(1.6%)	99% [(1.5%)
BREC-1125-174	At release		89.3% [(b) (4) (2.1%)	93.3% [(b) (4) (0.9%)	95.7% [(0.5%)
FPH-14-030 ‡	At release		91.8% [(1.2%)	94.4% [(1.1%)	96.2% [(0.9%)
PNNH	At release		89.5% [(1.2%)	94.1% [(0.9%)	96.6% [(0.9%)
BREC-1222-122	At release		90% [(b) (4) (2.7%)	95% [(b) (4) (1.7%)	97% [(b) (4) (1.1%)
AR5751	At release		81% [(b) (4)	93% [(b) (4)	96% [(b) (4)
AR5747	At release		93% [	100% [	101% [
AR5750	At release		92% [	98% [	101% [
AR5754	At release		99% [	102% [	102% [

† Dosed in clinical study 9785-CL-0014
‡ Dosed in clinical study MDV3100-19
RSD, relative standard deviation

Table 4: Dissolution data at 15, 20 and 30 min of the Enzalutamide Tablets 40 mg (Apparatus II Paddle, 50 rpm, 900 mL of pH 7.5 phosphate buffer, n=6)

Lot No.	Data at release or long-term stability		% Dissolved, n=6 vessels, (RSD) Mean [Min – Max]		
			15 min	20 min	30 min
TCKD	Bottle	At release (T=0)	98% (b) (4) (1.2%)	98% (b) (4) (1.2%)	98% (b) (4) (1.7%)
		3 months	98% (1.0%)	100% (1.0%)	99% (0.8%)
		6 months	98% (0.9%)	98% (1.5%)	99% (1.2%)
		9 months	98% (0.9%)	98% (0.8%)	99% (1.2%)
		12 months	100% (0.9%)	101% (1.3%)	101% (1.3%)
		18 months	99% (1.1%)	100% (1.5%)	100% (1.1%)
		24 months	98% (0.7%)	99% (0.6%)	100% (0.4%)
		36 months	96% (1.4%)	98% (1.2%)	98% (1.5%)
		48 months	96% (0.8%)	101% (1.1%)	100% (1.1%)
TCKF	Bottle	At release (T=0)	98% (1.0%)	100% (1.3%)	101% (0.8%)
		3 months	97% (0.8%)	98% (0.8%)	97% (1.6%)
		6 months	98% (1.3%)	100% (1.8%)	100% (1.6%)
		9 months	97% (1.0%)	99% (0.5%)	99% (1.1%)
		12 months	100% (0.9%)	101% (0.9%)	101% (1.3%)
		18 months	99% (1.3%)	100% (1.3%)	100% (0.9%)
		24 months	97% (0.8%)	99% (0.8%)	99% (2.2%)
		36 months	98% (0.7%)	98% (0.8%)	99% (0.7%)
		48 months	96% (1.2%)	99% (0.6%)	99% (0.6%)
TCKG	Bottle	At release (T=0)	99% (b) (4) (1.0%)	101% (b) (4) (1.2%)	101% (b) (4) (1.2%)
		3 months	99% (0.8%)	99% (1.1%)	100% (0.8%)
		6 months	99% (1.1%)	100% (1.5%)	99% (1.3%)
		9 months	98% (0.6%)	99% (0.8%)	99% (0.3%)
		12 months	100% (0.5%)	101% (0.6%)	101% (0.7%)
		18 months	97% (1.0%)	99% (1.1%)	100% (1.2%)
		24 months	100% (0.9%)	102% (1.1%)	102% (0.9%)
		36 months	98% (1.0%)	99% (0.8%)	99% (1.5%)
		48 months	96% (0.9%)	99% (0.6%)	100% (0.7%)
BREC-1222-119	At release		96% (1.2%)	99% (1.8%)	100% (0.7%)
TVHX	At release		96% (0.7%)	98% (0.8%)	99% (0.7%)
VBXM	At release		99% (1.2%)	100% (1.1%)	100% (0.9%)
VBXN	At release		99% (0.7%)	100% (0.8%)	99% (1.2%)
AR5748	At release		97% (b) (4)	99% (b) (4)	100% (b) (4)
AR5752	At release		98%	101%	101%
AR5749	At release		96%	98%	99%
AR5754	At release		99%	102%	102%

RSD, relative standard deviation

From the data presented in Tables 3 and 4 above, the proposed 40 mg tablets showed very rapid dissolution (mean dissolution >80% in 15 minutes) while the proposed 80 mg tablets showed rapid dissolution (mean dissolution >80% in 30 minutes) at release and under long-term stability condition for up to 48 months with no trends observed.

This Reviewer considers the proposed dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes" is acceptable because the following reasons: (i) the improved solubility from the (b) (4), which mitigated the risk of drug product quality/performance issues by the presence of (b) (4); (ii) the proposed dissolution method showed acceptable discriminating ability with regards to clinical formulations (showed in Figure 7 above), (b) (4) showed in Figures 8 and 9 above), and formulation variations (showed in Figure 10 above) at 30 minutes sampling time.

4. In vitro formulation bridging

All five development formulations (Tablet A, B, C, E and F) have been used in five in vivo BA/BE studies, while the pharmacokinetics (PK) parameters of the five development formulations have been evaluated by OCP, therefore, no additional in vitro studies are needed for bridging the five development formulations.

The composition of Tablet E is identical to the proposed TBM tablet, and lot # PMGY (same composition represents Tablet E and TBM tablets, per the Applicant) was used in the pivotal BE study (9785-CL-0014). The pivotal BE batch (lot # PMGY) and other commercial batches are produced from different manufacturing sites [(b) (4) (producing clinical and primary stability batches) vs. Pfizer Pharmaceuticals LLC (producing commercial batches, in Table 5 below) showed comparable dissolution data profiles (presented in Table 6 below). Therefore, the in vitro formulation bridging between pivotal BE Lot # PMGY and other commercial formulations has been established.

Table 5: Manufacturing sites for primary stability study, bioequivalence study and proposed commercial product

	Manufacturing site	
	(b) (4)	Tablets
Primary stability study & bioequivalence study (9785-CL-0014)		(b) (4)
Proposed commercial product		Pfizer Pharmaceuticals LLC

Table 6: Dissolution data of the proposed Enzalutamide Tablets, 80 mg and 40 mg

Lot No.	Manufacturing site of (b) (4)	Manufacturing site of Tablets
80 mg (PMGY)		(b) (4)
80 mg (AR5747)		Pfizer
80 mg (AR5750)		Pfizer
40 mg (TCKF)		(b) (4)
40 mg (AR5748)		Pfizer
40 mg (AR5749)		Pfizer

Strength	Lot No.	% Dissolved (% RSD)					f2 value †
		10 min	15 min	20 min	30 min	45 min	
80 mg	PMGY	75(5)	88(2)	93(1)	97(1)	98(1)	Not calculated ‡
	AR5747	44(33)	87(17)	98(3)	100(2)	100(2)	
	AR5750	83(17)	98(3)	100(2)	101(2)	101(2)	
40 mg	TCKF	96(1)	98(1)	98(1)	98(1)	98(1)	
	AR5748	101(1)	102(2)	102(2)	102(2)	102(1)	
	AR5749	101(2)	102(2)	102(2)	101(2)	101(2)	

† f_2 value was calculated compared to primary stability study products data.
‡ More than 85% dissolved within 15 minutes, evaluation of f_2 value is not required.

5. Biowaiver

In current NDA, the Applicant submitted a formal biowaiver request for the proposed lower strength drug product, Enzalutamide Tablets, 40 mg, in M.1.12.15. The following supportive information is submitted to support the biowaiver, summarized as:

(1) The proposed higher strength Enzalutamide Tablets 80 mg (2x80 mg tablets = 160 mg dose) and the approved Enzalutamide Capsules 40 mg (4x40 mg capsules = 160 mg dose) are found BE under fasting and fed conditions in the pivotal BA/BE study (9785-CL-0014).

(2) The compositions of the proposed Enzalutamide Tablets 80 mg and 40 mg are (b) (4), as showed in Table 7 below. Both strengths products have same dosage form i.e. immediate release tablets.

Table 7: Composition of the proposed Enzalutamide Tablets 80 mg and 40 mg

Component	Function	Reference to Quality Standard	Target amount per 80 mg Tablet (mg)	Target amount per 40 mg Tablet (mg)
Enzalutamide †	Active Ingredient	Module 3.2.S.4.1 of NDA 203415	80.0	40.0
Hypromellose Acetate Succinate †	(b) (4)	[Module 3.2.P.4.1]	(b) (4)	
(b) (4)		NF		
Microcrystalline Cellulose		NF		
Colloidal Silicon Dioxide		NF		
Croscarmellose Sodium		NF		
Magnesium Stearate		NF		
Core Tablet Weight				
(b) (4) Yellow (b) (4) (b) (4)	(b) (4) Color Film Coat (b) (4)	[Module 3.2.P.4.1]		
		USP	N/A	N/A
Total Tablet Weight			669.5	334.75

(b) (4)

N/A, not applicable; NF, National Formulary; (b) (4) USP, United States Pharmacopeia

(3) The manufacturing process (b) (4) and manufacturing site are same for the proposed 40 mg and 80 mg Enzalutamide Tablets.

(4) The proposed 40 mg tablets showed comparable dissolution data profiles with the 80 mg tablets in multi-media (b) (4) and QC medium (pH 7.5 phosphate buffer), as presented in the following Figures 13 to 16, and Table 8, by using the same dissolution conditions (USP apparatus II paddle, 50 rpm, 900 mL of media).

Figure 13: Dissolution profiles of Enzalutamide Tablets 80 mg and 40 mg in (b) (4)

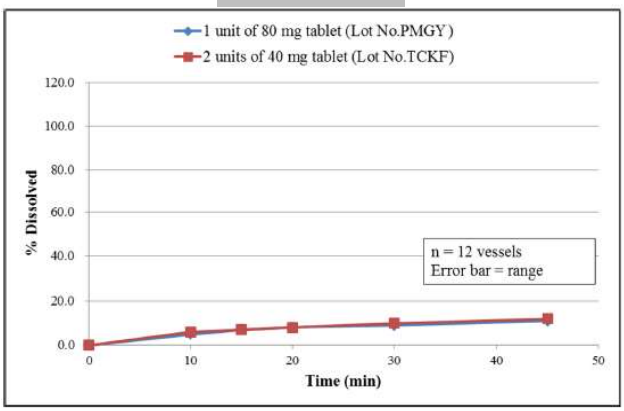


Figure 14: Dissolution profiles of Enzalutamide Tablets 80 mg and 40 mg in (b) (4)

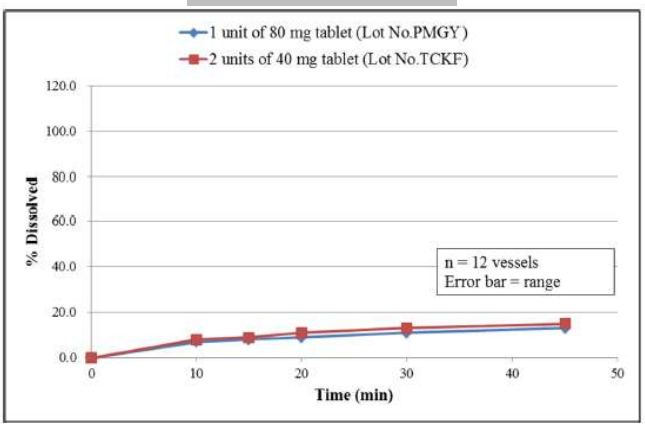


Figure 15: Dissolution profiles of Enzalutamide Tablets 80 mg and 40 mg in (b) (4)

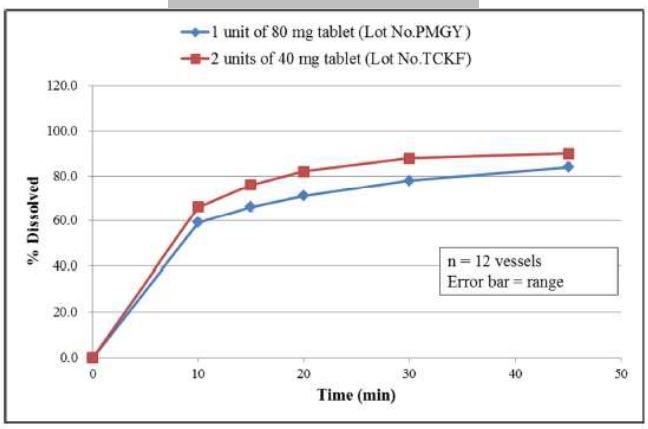


Figure 16: Dissolution profiles of Enzalutamide Tablets 80 mg and 40 mg in pH 7.5 phosphate buffer (QC method)

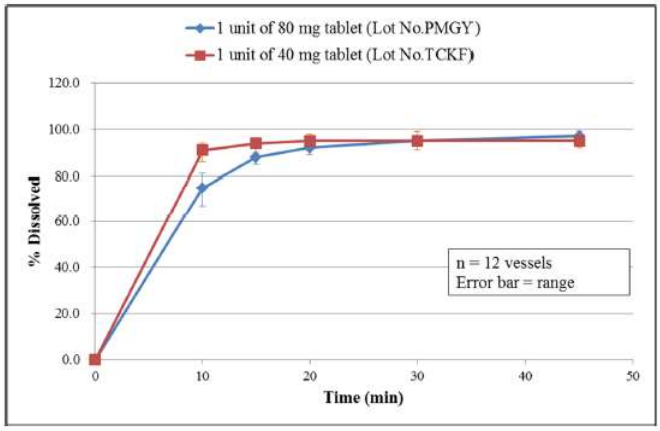


Table 8: *f2* values of dissolution profiles between Enzalutamide Tablets 80 mg and 40 mg

Dissolution Medium	Sample (Unit per vessel)	% Dissolved (% RSD)					f_2 value
		10 min	15 min	20 min	30 min	45 min	
(b) (4)	80 mg tablets (1 unit)	5 (0)	7 (4)	8 (0)	9 (0)	11 (0)	94.9
	40 mg tablets (2 units)	6 (0)	7 (0)	8 (6)	10 (0)	12 (2)	
	80 mg tablets (1 unit)	7 (6)	8 (0)	9 (4)	11 (3)	13 (0)	85.5
	40 mg tablets (2 units)	8 (7)	9 (3)	11 (3)	13 (0)	15 (0)	
	80 mg tablets (1 unit)	59 (1)	66 (1)	71 (1)	78 (1)	84 (1)	52.1
	40 mg tablets (2 units)	66 (1)	76 (1)	82 (1)	88 (1)	90 (1)	
pH 7.5 Phosphate Buffer	80 mg tablets (1 unit)	75 (6)	88 (2)	92 (1)	95 (1)	97 (1)	Not calculated †
	40 mg tablets (1 unit)	91 (2)	94 (2)	95 (2)	95 (2)	95 (2)	

Note: Underline indicates data used for dissolution comparison. Time-points for evaluation were determined based on the dissolution profile of reference product (80 mg tablets).

† More than 85% dissolved within 15 minutes, evaluation of f_2 value is not required.

(5) The results from the analyses with AUC_{120h}, AUC_{24h} and C_{max} suggested dose-proportional pharmacokinetics of the daily dose range of 30 to 600 mg enzalutamide according to the OCP review for the approved capsules (NDA 203415, dated 08/28/2012).

Overall, this Reviewer considers that all the above data information supported the biowaiver request of the proposed Enzalutamide Tablets, 40 mg. Therefore, the biowaiver request is granted per 21 CFR 320.22(d)(2), as the pivotal BA/BE study (9785-CL-0014) has been found acceptable by OCP.

APPENDIX 1
Biopharmaceutics Information Request and Applicant's Response

Biopharmaceutics IR (conveyed on 03/23/2020):

Symbols in Figures 6 A and B located in the M.2.7.1, page 32, showing the relationship between Mean % dissolved at 20 minutes versus AUC_{inf} and C_{max}, respectively, for different formulations, are missing. Please correct this oversight and re-submit this figure.

Applicant's response through email on 03/23/2020:

The symbols the reviewer requested are the tablet labels in the figure. For instance, Tablet A is 32.8 mean %dissolved and 93.65 AUC_{inf} GMR. The center of the 'Tablet A' text in the plot are the coordinates. This was an intentional design to improve the readability of the plot. The actual coordinates of the tablet labels are in the table below the figure. The same is true for the Cmax plot (B).

Biopharmaceutics' comments conveyed through email on 03/24/2020:

We have no further questions. Thanks for the clarification.

Mei Ou

Digitally signed by Mei Ou
Date: 5/08/2020 01:22:04PM
GUID: 54ca9d7000073c57d2eb7cc6e42c05bb

Banu Zolnik

Digitally signed by Banu Zolnik
Date: 5/08/2020 01:45:22PM
GUID: 508da7270002a568e175a2c0dd90f334

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/

XIAOHONG CHEN
07/14/2020 09:57:26 AM