CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210951Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210951
Review #1

Drug Name/Dosage Form	ERLEADA® (apalutamide) Tablet
Strength	60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Janssen Biotech, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Rolling submission 0002	09/29/2017	API/DP/Process/Biopharm/Facility
Original NDA 0003	10/10/2017	API/DP/Process/Biopharm/Facility
Quality Amendment 0009	11/06/2017	Process
Quality Amendment 0011	11/20/2017	DP
Quality Amendment 0012	12/04/2017	DP
Quality Amendment 0020	12/20/2017	DP
Quality Amendment 0023	12/22/2017	Process
Quality Amendment 0024	12/22/2017	API
Quality Amendment 0027	1/10/2018	Environmental Assessment
Labeling/Container-Carton 0028	1/11/2018	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rajan Pragani	CDER/OPQ/ONDP/DNDAPI
Drug Product	Xing Wang	CDER/OPQ/ONDP/DNDP1
Process	Lixia Cai	CDER/OPQ/OPF/DPA1
Microbiology	N/A	
Facility	Zhong Li	CDER/OPQ/OPF/DIA
Biopharmaceutics	Banu Zolnik	CDER/OPQ/ONDP/DB

Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	OGROP/ORA/OMPTO/OPQO/DPQP/PQIB
Environmental	James Laurenson	CDER/OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4) [redacted]	Type IV	[redacted]	(b) (4) [redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
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	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104676	Initial IND was submitted on 2/17/2009

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			

CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

CMC information provided for ERLEADA (apalutamide) tablets in this NDA has been review by the quality review team in the Office of Pharmaceutical Quality, and is found to be acceptable. The review team recommended approval for the NDA from the product quality standpoint.

A shelf life of 24 months is granted for ERLEADA (apalutamide) tablets stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	ERLEADA (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC).
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	Recommended dose: ERLEADA 240 mg (four 60 mg tablets) administered orally once daily. Swallow tablets whole. ERLEADA can be taken with or without food.
Alternative Methods of Administration	None.

B. Quality Assessment Overview

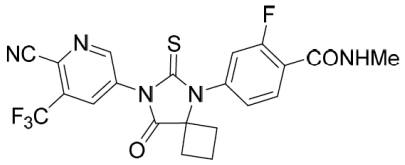
Drug substance

- Chemical Name and Structure:

Name: Apalutamide

Chemical Name: 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-*N*-methylbenzamide

Structure:



Molecular Weight: 477.43

The drug substance is a white to slightly yellow powder.

Apalutamide drug substance does not have a chiral center. The drug substance melts at about 194-196 °C. The drug substance is practically insoluble in aqueous media over a wide range of pH values and practically insoluble to very soluble in organic solvents. The drug substance has a dissociation constant pK_a of 9.7 (acidic carboxamide moiety). The solubility experiments show that it is unstable to strong base (pH >11)

The drug substance exhibits polymorphism, with (b) (4) The (b) (4) was chosen to be the form for drug development. (b) (4) . The drug substance is nonhygroscopic.

The drug substance is synthesized in (b) (4) steps from the (b) (4) regulatory starting materials that were agreed by the Agency in the Type C Meeting on 29 July 2016 (IND 104676 SN 0283). The manufacturing process description, raw materials controls and process controls are adequate to consistently produce the API that meet the drug substance specification. The elemental impurities and solvents are controlled per ICH guidance. The potential mutagenic impurities are controlled through demonstration of impurity purge study.

The drug substance has been adequately characterized. The analytical methods of the drug substance regulatory specification to control the quality of the drug substance are validated to ensure quality control. The stability data demonstrate that the drug substance is stable over the proposed retest period of (b) (4) months.

Drug product

The drug product is an immediate release, oblong shaped, greenish film-coated (FC) tablet for oral administration. The tablet is debossed with "AR 60" on one side and contains 60 mg of apalutamide drug substance. The tablet is made from (b) (4)

The tablet contains 60 mg of apalutamide drug substance (as (b) (4) and commonly used compendial excipients: colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose and magnesium stearate. The drug product is packaged in 160 cc HDPE bottles containing 120 count tablets with a silica gel desiccant and (b) (4) closure.

The drug product specifications consist of appearance, identity, assay, individual and total degradation products, uniformity of dosage units, dissolution, (b) (4), (b) (4) and microbial purity. The drug product specification is deemed adequate to assure identity, strength, purity, and quality of apalutamide tablets.

Full term stability data of (b) (4) supports a shelf life of (b) (4)-month for the (b) (4) stored in the proposed commercial packaging. Stability data of drug product batches manufactured with "fresh" and "aged" (b) (4) show no trend or OOS. Per ICH Q1E and stability data provided, it is acceptable to grant 24-month shelf-life for apalutamide tablets packaged in the commercial container closure system and stored at controlled room temperature. In addition, control strategy and stability information provided in the NDA submission support the proposal to calculate the expiry date of apalutamide tablets from (b) (4)

Drug Product Manufacturing Process

(b) (4)

(b) (4) All process related deficiencies have been addressed satisfactorily.

Facility

Based on compliance history review and considering the proposed manufacturing to be conducted at each of the sites, the Drug Substance (FEI# 1033845 and FEI# 3002807337) and Drug Product (FEI# 3002942061, FEI# 3003164454 and FEI# 3007543295) Manufacturing facilities, are deemed acceptable. Therefore, no Pre-approval inspection (PAI) is to be performed for all two manufacturing sites provided in the NDA.

Biopharmaceutics

The proposed dissolution method and acceptance criterion are acceptable. The dissolution method can discriminate the presence of (b) (4) material beyond (b) (4)%; the dissolution method is over discriminating for the selected range of particle size ((b) (4) .

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
USP Apparatus II	75 rpm	900mL	37°C ± 0.5°C	0.25% (w/v) SLS in 0.05 M Sodium Phosphate Buffer, pH 4.5	Q= (b) (4)% in 30 minutes

The Applicant's mechanistic absorption model indicates that up to (b) (4)% (b) (4) (b) (4) in the drug product does not decrease the bioavailability of apalutamide. Since the Applicant controls (b) (4) in the (b) (4) and the drug product, there are no potential risks that the (b) (4) material ever exceeding this level. The results of the submitted absorption modeling serve as supportive data for the proposed limit of (b) (4) in apalutamide tablets.

During clinical studies, the subjects received tablet formulations as well as the capsule formulations. The Applicant conducted a relative BE study (Study 1011) between the capsule and tablet formulations. The Office of Clinical Pharmacology Reviewer Dr. Wentao Fu concludes that based on the BA study PCR1011 results, there is no clinically relevant exposure differences between these two formulations (see the Clinical Pharmacology review).

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

D. Final Risk Assessment (see Attachment)

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.

29-Jan-2018

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CHAPTER IV: Labeling

Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	ERLEADA® (apalutamide)	Adequate
Dosage form, route of administration	Tablets For Oral Administration	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Film-coated tablet 60 mg	Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

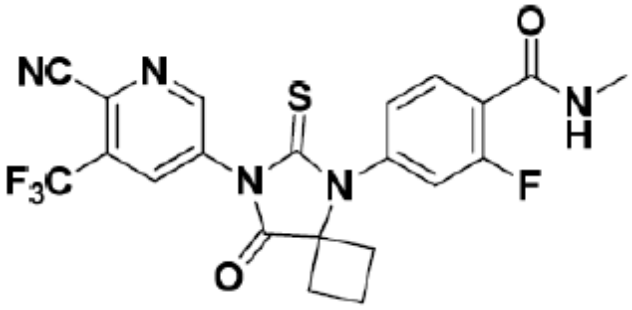
Tablet: 60 mg, slightly yellowish to greyish green oblong film-coated tablets, debossed with "AR 60" on one side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	60 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	slightly yellowish to greyish green oblong tablets, debossed with "AR 60" on one side.	Adequate

Conclusion: Conveyed to DOP1 review team during labeling meeting.

#11: Description (21CFR 201.57(c)(12))

Apalutamide, the active ingredient of ERLEADA, is an androgen receptor inhibitor. The chemical name is (4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide). Apalutamide is a white to slightly yellow powder. Apalutamide is practically insoluble in aqueous media over a wide range of pH values.The molecular weight is 477.44 and molecular formula is $C_{21}H_{15}F_4N_5O_2S$. The structural formula is:



ERLEADA (apalutamide) is supplied as film-coated tablets for oral administration containing 60 mg of apalutamide. Inactive ingredients of the core tablet are: colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose.

The tablets are finished with a commercially available film-coating consisting of the following excipients: iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	ERLEADA	Adequate
Dosage form and route of administration	film-coated tablets for oral administration	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Free base, not salt	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)		N/A
Pharmacological/ therapeutic class	androgen receptor inhibitor	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Not provided	Added

Conclusion: Conveyed to DOP1 review team during labeling meeting.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

ERLEADA (apalutamide) 60 mg film-coated tablets are slightly yellowish to greyish green, oblong-shaped tablets debossed with "AR 60" on one side. ERLEADA 60 mg tablets are available in bottles of 120 tablets. Each bottle contains silica gel desiccant.

NDC Number 59676-600-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store in the original package. Do not discard desiccant. Protect from light and moisture.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Tablets: 60 mg	Adequate
Available units (e.g., bottles of 100 tablets)	bottles of 120 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Store in the original package. Do not discard desiccant. Protect from light and moisture.	Adequate
Storage conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate

Conclusion: Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Provided	Adequate

Conclusion: Adequate

Container Labeling

(b) (4)

[redacted]

Conclusion: Adequate

Carton Labeling

Note: The opaque blister is a physician sample package and is not intended for commercial distribution.

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tem	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ERLEADA™ (apalutamide) Tablets	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	60 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	For oral use thus not required	Adequate
Net contents* (21 CFR 201.51(a))	Provided	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	For oral use thus not required	Adequate
Lot number per 21 CFR 201.18	Reserved space	Adequate
Expiration date per 21 CFR 201.17	Reserved space	Adequate
"Rx only" statement per 21 CFR	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Not Provided	Physician sample package, not for commercial distribution.
Name of manufacturer/distribut	Provided	Adequate

or (21 CFR 201.1)		
Others		Adequate

Reviewer's Assessment: Adequate

List of Deficiencies: None

Primary Drug Product Reviewer Name and Date:

Xing Wang, Ph.D., ONDP/DNDPI/NDPBII

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

Anamitro Banerjee, Ph.D., Acting Branch Chief, ONDP/DNDPI/NDPBII

Xing Wang

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Anamitro Banerjee

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CHAPTER VII

BIOPHARMACEUTICS

Application No: NDA-210951-ORIG-1

Drug Product Name / Strength: Erleada® (apalutamide) Tablets, 60 mg

Route of Administration: Oral

Applicant Name: Janssen Research and Development LLC.

List Submissions being reviewed:
Original dated 9/11/2017

EXECUTIVE SUMMARY

Background:

Janssen Research and Development LLC is seeking approval for Erleada® (apalutamide) Tablets, 60 mg for the treatment of patients with non-metastatic castration-resistant prostate cancer under section 505 (b) (1) of the Federal Food, Drug, and Cosmetic Act.

Review Summary:

This Biopharmaceutics Review evaluated the overall data supporting; **1)** The proposed dissolution method, **2)** The proposed dissolution acceptance criterion, and **3)** The mechanistic absorption model to support the proposed clinically relevant specifications.

- ***DISSOLUTION METHOD AND ACCEPTANCE CRITERION***

The proposed dissolution method and acceptance criterion are acceptable. The dissolution method can discriminate the presence of (b) (4) material beyond (b) (4)%; the dissolution method is over discriminating for the selected range of particle size ((b) (4) .

Below is the approved dissolution method and the acceptance criterion.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
USP Apparatus II	75 rpm	900mL	37°C ± 0.5°C	0.25% (w/v) SLS in 0.05 M Sodium Phosphate Buffer, pH 4.5	Q= (b) (4)% in 30 minutes

- ***THE MECHANISTIC ABSORPTION MODEL TO SUPPORT CLINICALLY RELEVANT SPECIFICATIONS***

It is important to recognize that mechanistic absorption modeling is now being utilized as an important tool to support selection of clinically relevant specifications. This review includes the overview of this model. The Applicant's mechanistic absorption model indicates that up to (b) (4)% (b) (4) (b) (4) in the drug product does not decrease the bioavailability of apalutamide. Since the Applicant controls (b) (4) in the (b) (4) and the drug product, there are no potential risks that the (b) (4) material ever exceeding this level. It is pertinent to mention that results of the submitted absorption modeling serve as supportive data for the proposed limit of (b) (4) in apalutamide tablets. Any future application of the model for other purposes will be assessed separately with its supporting data.

- ***BRIDGING OF FORMULATIONS***

Clinical development started with a 30 mg liquid filled capsule formulation. The Applicant changed the tablet dosage form which is the to-be-marketed formulation because of stability issues and higher capsule pill burden observed with the capsules. During clinical studies (Phase1/2, and Phase 1: Studies -001, 1008, 1010 and Phase 3: Spartan Study 003), the subjects received tablet formulations as well as the capsule formulations. The Phase 1 hepatic impairment, cardiac and drug interaction studies (Study #1018, 1019, 1020, and 1021) were only conducted with the tablet formulation: The Applicant conducted a relative BE study (Study 1011) between the capsule and tablet formulations. The Office of Clinical Pharmacology Reviewer Dr. Wentao Fu concludes that based on the BA study PCR1011 results, there is no clinically relevant exposure differences between these two formulations (see the Clinical Pharmacology review). Therefore, adequate bridging of the clinical and the proposed commercial formulations has been demonstrated.

- ***BIOWAIVER REQUEST***

A biowaiver request is not needed since there is only one strength of the proposed drug product.

- ***OVERALL REVIEW RECOMMENDATION***

From the Biopharmaceutics perspective, NDA 210951 for Erleada® (apalutamide) Tablets, 60 mg, is recommended for APPROVAL.

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Banu S. Zolnik, PhD ***1/26/2018***

Secondary Reviewer Name and Date:

Okpo Eradiri, PhD ***1/26/2018***

BIOPHARMACEUTICS ASSESSMENT

➢ BACKGROUND:

Apalutamide is a next generation, orally administered androgen inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer. The Application received a Fast Track designation.

➢ DRUG SUBSTANCE:

Apalutamide is insoluble in aqueous media over the pH range of 1-12 (Table 1). The Applicant stated that the permeability of apalutamide across Caco-2 cells is high with a P_{app} A-to-B value of 42.3 $X10^{-6}$ cm/s. It should be noted that (i.e., P_{app} A-to-B $\geq$ 1.0 $X10^{-6}$ cm/s, and also higher than the high permeability marker propranolol of P_{app} A-to-B value 17.3 $X10^{-6}$ cm/s). The absolute bioavailability of a single 240 mg dose of apalutamide capsule was reported to be approximately 100% (study report ARN-509-006). Based on these findings, the drug substance is classified as BCS class II (Low solubility, High Permeability) by the Applicant.

Table 1. The solubility of Apalutamide in aqueous media as a function of pH at room temperature

Medium	Solubility (g/100 mL)	pH of Solution	Solubility Description[a]
Demineralized Water	<0.001	7.5	Practically insoluble
0.1 N HCl	<0.001	1.1	Practically insoluble
0.01 N HCl	<0.001	2.0	Practically insoluble
Citrate Buffer pH 2 (Citric Acid + NaOH + HCl)	<0.001	2.0	Practically insoluble
Citrate Buffer pH 5 (Citric Acid + NaOH)	<0.001	5.0	Practically insoluble
Phosphate Buffer pH 7 (KH_2PO_4 + Na_2HPO_4)	<0.001	7.0	Practically insoluble
Borate Buffer pH 9 (Boric Acid + NaOH + KCl)	<0.001	9.0	Practically insoluble
Phosphate Buffer pH 12 (Na_2HPO_4 + NaOH)	NR	11.9	NR
0.1 N NaOH	NR	12.4	NR

[a] Defined in USP and Ph. Eur.

NR = No result because of degradation of the drug substance

➢ DRUG PRODUCT:

The proposed drug product is an immediate release film coated tablet. The proposed drug product is made from a (b) (4) . The composition information is shown in Appendix 1.

➢ DISSOLUTION METHOD

The dissolution method proposed as a quality control test for the proposed drug product is summarized below.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP Apparatus II	75 rpm	900mL	37°C ± 0.5°C	0.25% (w/v) SLS in 0.05 M Sodium Phosphate Buffer, pH 4.5

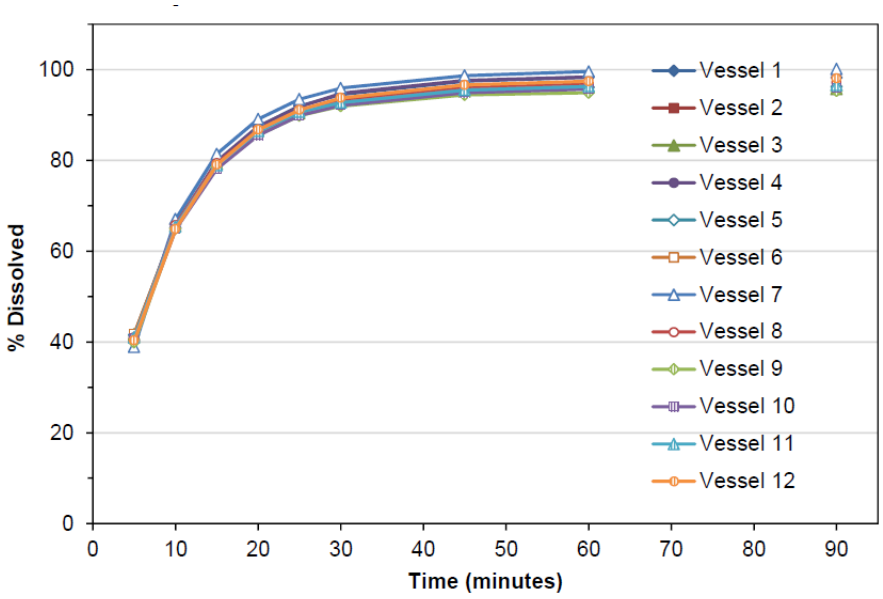


Figure 1. Dissolution profiles of apalutamide tablets using the proposed dissolution method [USP II, 900 mL 0.25% SLS in 0.05M sodium phosphate buffer, pH 4.5, 75 rpm]

1. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

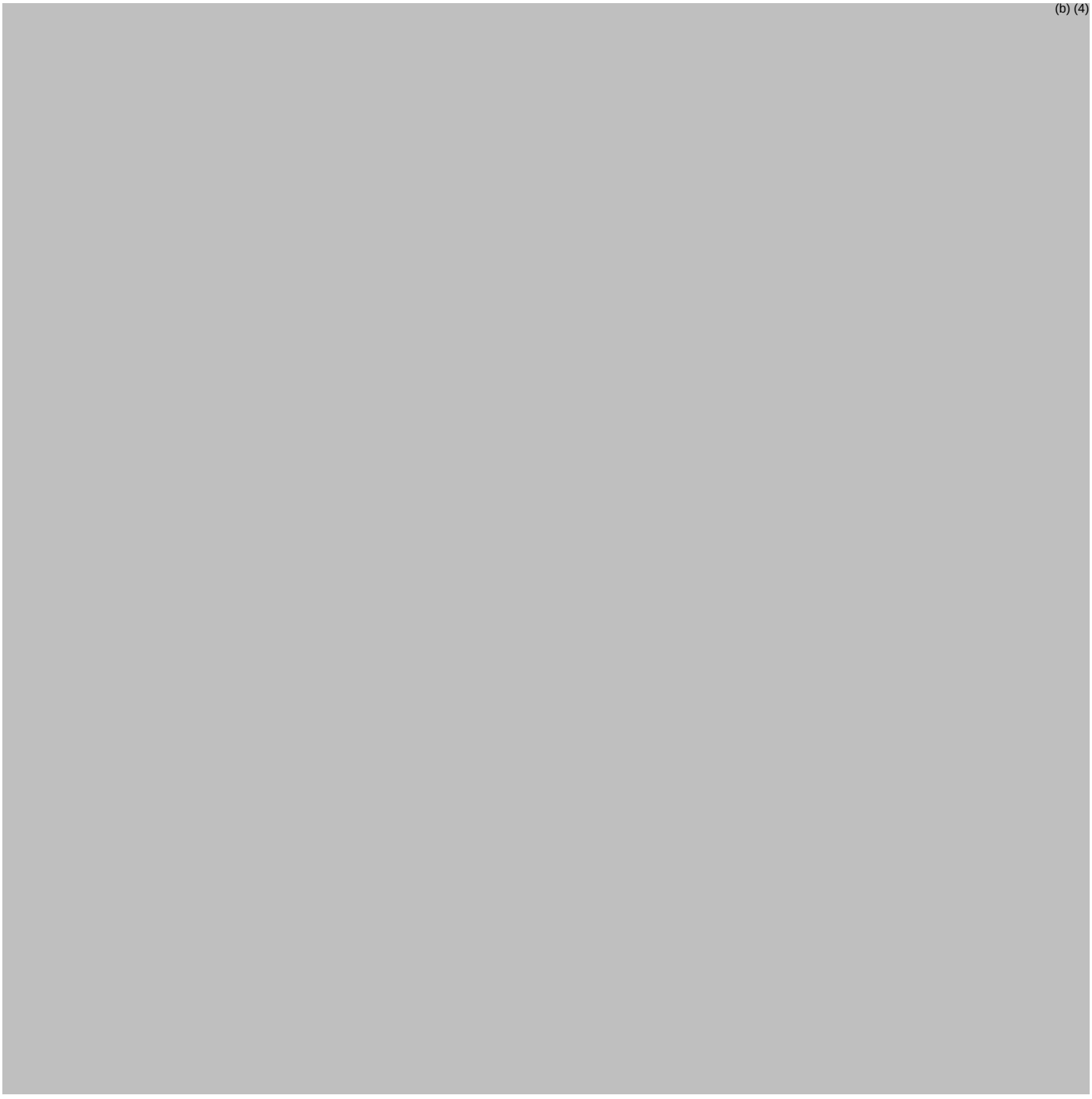
The Applicant investigated three different dissolution methods (Method A, Method B, and the proposed dissolution method) during the method development.

Method A (b) (4)

The Applicant

investigated the discriminating ability of all three dissolution methods but only the experiments conducted with the proposed regulatory method is presented in this review; experimental details for Methods A and B can be found via the following link: \\cdsesub1\evsprod\nda210951\0002\m3\32-body-data\32p-drug-prod\active-film-coated-tablet\32p2-pharm-dev\pharmaceutical-development-ds-tec-106755-60mg.pdf).

(b) (4)



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2. What data are available to support the discriminating ability of the dissolution method?

The Applicant investigated the discriminating ability of the proposed dissolution method towards (b) (4) particle size distribution, the presence of (b) (4) (b) (4), tablet hardness and drug product changes during storage.

a. Discriminating ability for particle size distribution

The Applicant manufactured target batch (with a particle size (b) (4)) and four additional batches with varying particle sizes (Table 4). The comparative dissolution profiles are shown in Figure 10.

Table 4. Drug product batches with varying particle size used to demonstrate the discriminating ability of the proposed dissolution method.

Treatment	DP Batch	(b) (4) Batch	DS Batch	Label	Particle Size (µm)		
					d_v10	d_v50	d_v90
B	15B20/G023	14L04/G017	G503FPB-14-002	Fine	(b) (4)		
C	15B25/G023	15A28/G017	G503FPB-14-002	Medium Fine			
A	15B27/G023[a]	15B09/G017	G503FPB-14-002	Target			
D	15C02/G023	15B25/G017	G503FPB-14-002	Medium Coarse			
E	15B23/G023	15A19/G017	G503FPB-14-002	Coarse			

DP = drug product; (b) (4) = (b) (4); DS = drug substance; [a] target

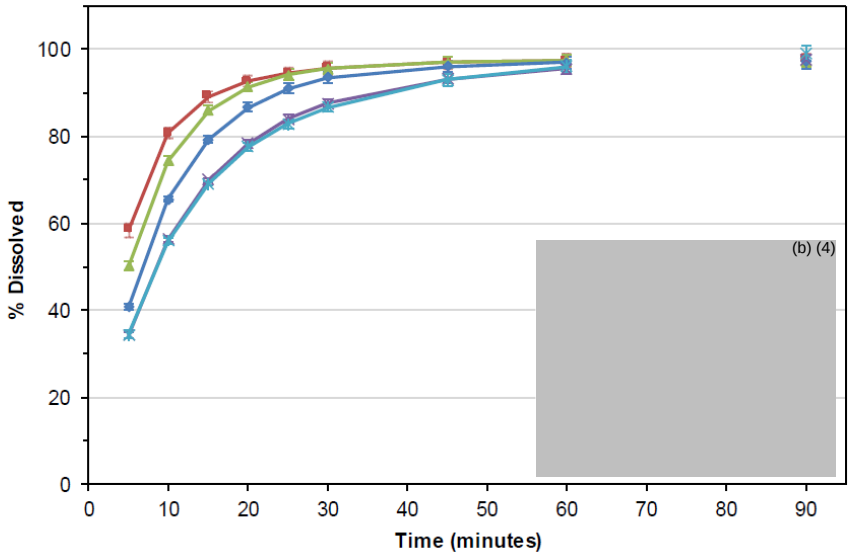

Figure 10. Dissolution Profiles of the Proposed Drug Product Produced with Different Particle Size (Fine: (b) (4) µm, Medium Fine: (b) (4) µm, Target: (b) (4) µm, Medium Coarse: (b) (4) µm, and Coarse: (b) (4) µm) using the Proposed Dissolution Method

The Reviewer's calculated f2 similarity factor between the target and aberrant batches in Table 5 indicate that the dissolution profiles of the aberrant batches with particle size medium fine, medium coarse and coarse are similar to that of the target batch (as f2 values equal and greater than 50). The dissolution profile of the aberrant batch with fine particle size is not similar to that of target batch (as f2 value is less than 50). The proposed dissolution method is able to discriminate for the fine particle size batch. It should be noted that these four batches were also used in the Bioavailability Study 56021927PCR1015 and study results showed comparable bioavailability profiles shown in Figure 11. This indicates that the proposed dissolution method over discriminates for the drug product batches with varying particle sizes.

Table 5. Reviewer's Calculated f2 values between the target and the aberrant batches with varying particle size

f2 values				
For Particle Size	**Fine**	**Medium Fine**	**Medium Coarse**	**Coarse**
Target	47	59	57	57

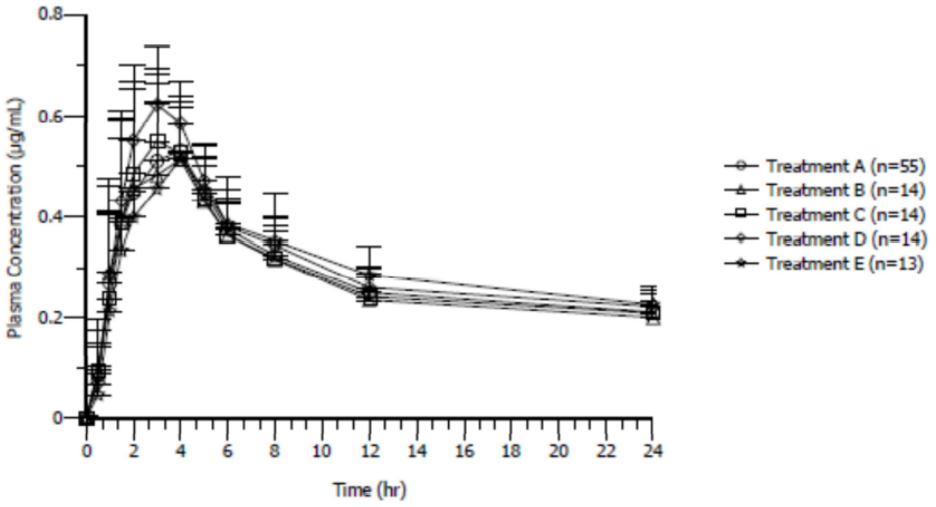

Figure 11. The mean plasma concentration time curves after administration of a single dose drug product batches with different (b) (4) particle size distribution

b. <u>Discriminating ability for the presence of (b) (4) (b) (4)</u>.

The proposed drug product is manufactured with the (b) (4) apalutamide (b) (4)). Therefore, there is a potential (b) (4) To address this potential issue, the Applicant manufactured drug products spiked with (b) (4) (b) (4) (Table 6). The comparative

dissolution profiles of drug products spiked with (b) (4) (b) (4) and control (not spiked) are shown in Figure 12.

Table 6. Drug product batches with spiked with (b) (4) (b) (4) to demonstrate the discriminating ability of the proposed dissolution method.

DP Batch	Amount of Spiked (b) (4) (b) (4) (b) (4) (%w/w)
JNJ-56021927-n001-01385 (b) (4)	(b) (4)
JNJ-56021927-n001-01385	
JNJ-56021927-n001-01385/	
JNJ-56021927-n001-01385/	
JNJ-56021927-n001-01385/	
JNJ-56021927-n001-01385/	

DP = drug product

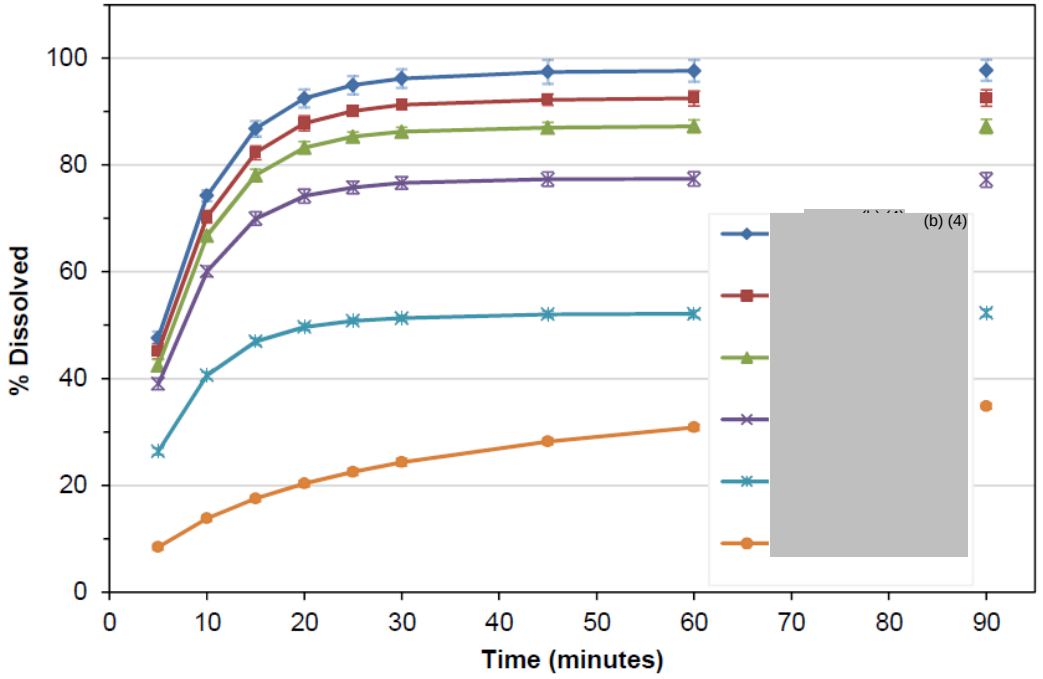

Figure 12. Evaluation of the discriminating ability of the dissolution method for different amounts of spiked (b) (4) (b) (4) in the drug product batches ((b) (4)) using the proposed dissolution method

The Reviewer's calculated f2 similarity factor the target and aberrant batches is shown in Table 7.

Table 7. Reviewer's Calculated f2 values between 0% and the aberrant batches with spiked (b) (4) (b) (4)

	f2 values				
(b) (4)	(b) (4)				
	74	41	42	23	15

The f2 values indicate that the dissolution method is able to discriminate the presence of (b) (4) (b) (4) (b) (4) in the drug product as f2 values are less than 50. The dissolution profile of the aberrant batch with (b) (4) is similar to that of target batch (f2 value is greater than 50).

The Applicant is controlling the presence of (b) (4) and in the drug product (with the acceptance criterion of less than (b) (4)% using (b) (4) method).

The Applicant also investigated the discriminating ability of the dissolution method for tablet hardness, and film coating, the proposed dissolution method is not discriminating for these parameters (data not shown but can be found on the following link on pages 58-63 \\cdsesub1\evsprod\nda210951\0002\m3\32-body-data\32p-drug-prod\active-film-coated-tablet\32p2-pharm-dev\pharmaceutical-development-ds-tec-106755-60mg.pdf.)

3. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The Applicant provided adequate information to support the validity of the analytical methods used to evaluate the dissolution samples of apalutamide. The detailed information is included in the following link: \\cdsesub1\evsprod\nda210951\0002\m3\32-body-data\32p-drug-prod\active-film-coated-tablet\32p5-contr-drug-prod\32p53-val-analyt-proc\validation-analyt-procedures-ds-val-118211-60mg.pdf.

- ***PROPOSED DISSOLUTION ACCEPTANCE CRITERION:***

The Applicant proposed the following dissolution acceptance criterion.

Proposed Dissolution Acceptance Criterion
Q = (b) (4)% in 30 minutes

4. Are there any in silico modelling data/approach to justify/support the proposed dissolution method?

The Applicant submitted a virtual bioequivalence trial using a mechanistic absorption model to compare the bioavailability of drug product batches with different amounts of spiked (b) (4) (b) (4) The results of the 10 virtual trials show that drug product batches with up to (b) (4)% (b) (4) (b) (4) are bioequivalent while drug product batches with more than (b) (4)% (b) (4) (b) (4) are not bioequivalent.

The Applicant submitted the mechanistic absorption model to support clinically relevant specification in the following link \\cdsesub1\evsprod\nda210951\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nm-crpc\5354-other-stud-rep\ds-tec-105917\ds -tec-105917.pdf and Apalutamide mechanistic model of absorption-modeling and simulation report can be found in \\cdsesub1\evsprod\nda210951\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nm-crpc\5354-other-stud-rep\ds-tec-97917\ds-tec-97917.pdf

The overview of the Applicant's approach in PBPK modeling to support the clinically relevant specification as is follows:

A. Relative BA studies

The Applicant conducted four relative bioavailability studies where the impact of change in dosage form and process, (b) (4) type and amount, particle size, manufacturing process, dose strength selection, scaling and site transfer (The overview of the each study design can be found in Appendix 2).

- Study PCR1007: Relative BA study of seven tablet formulations to the capsule formulation
- Study PCR1011: Relative BA study of three tablet formulations to the capsule formulation
- Study PCR1015: Crossover study of tablet formulation with varying particle size distribution
- Study PCR1017: Crossover study of (b) (4) tablet formulation from different manufacturing sites.

B. **The development of physiology based dissolution testing (PBDT)**

It should be noted that PBDT is not the QC dissolution method described in this review. The PBDT below is utilized in model building as the biorelevant media:

(b) (4)

C. Mechanistic model of absorption

The Applicant validated the model based on the physico-chemical properties, the PBDT profiles of each formulations used in each clinical study and the BA study results.

D. Modeling and Simulation

The Applicant performed modeling and simulations using Gastroplus version 9. The data from the in vitro BE trails exported to Excel [redacted] The BE parameters of the virtual trial populations were calculated in Pharsight Phoenix.

RESULTS

1. PBDT profiles

Figure 13 shows the physiology based dissolution profiles of formulations used in the BA study PCR 1007 used as one of the input parameters in building the model as an example. The PBDT profiles of the formulations used in the other clinical studies are not shown but can be found on the page 24-25 in the following link \\cdsesub1\evsprod\nda210951\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nm-crpc\5354-other-stud-rep\ds-tec-97917\ds-tec-97917.pdf. There is a clear differences in the dissolution/precipitation kinetics of [redacted] (black square, and orange circles) and the [redacted] formulations. The [redacted] formulation has shown precipitation in the PBDT medium while [redacted] formulation is able to maintain apalutamide in the super saturation state in PBDT FaSSIF medium. It is important to recognize that due to absorption kinetics in vivo, in vivo precipitation is not likely.

Figure 13. Physiology based dissolution profiles of apalutamide formulations with different formulations used in the study PCR1007 (see Appendix 2 for information on each formulation)

2. PBDT INPUT PARAMETERS: USE OF Z FACTOR

Z factor was calculated using Gastroplus which is a measure for dissolution rate overtaking into account, particle size, drug density and diffusion coefficient as described in the following equation (D: diffusion coefficient; ρ: drug density; h: diffusion layer thickness; r: radius spherical particles):

$$\frac{dA_d}{dt} = \frac{3D}{\rho hr} \times A_0 \left(\frac{A_s}{A_0}\right)^{2/3} \left(C_s - \frac{A_d}{V}\right)$$

Table 8. Overview of the apalutamide oral formulations used to build and validate the model of absorption.

Study	Formulation	Batch	Dose	Solubility SGF mg/ml	Solubility FaSSIF mg/ml	Solubilization Ratio ---	z-factor ml/mg/s
---	Liquid filled capsules 30 mg	12JM-335					
PCR1007		13K18/G012	240 mg				
PCR1007		13K19/G013	240 mg				
PCR1007		13K21/G009	240 mg				
PCR1007		13K25/G008	240 mg				
PCR1007		13K26/G007	240 mg	0.029	0.164		
PCR1007		13L02/G010	240 mg				
PCR1007		13L03/G011	240 mg				
PCR1011		14E14/G024	240 mg				
PCR1011		14E20/G023	240 mg	0.028	0.153		
PCR1011		14E21/G025	240 mg				
PCR1015		15B20/G023	60 mg				
PCR1015		15B23/G023	60 mg				
PCR1015		15B25/G023	60 mg				
PCR1015		15B27/G023	60 mg	0.027	0.121		
PCR1015		15C02/G023	60 mg				
PCR1017		15B19/G023	60 mg	0.025	0.132		
PCR1017		15E26/G023	60 mg	0.026	0.148		
PCR1017		15DG0036X SB2 M	60 mg	0.026	0.149		

3. MODEL VALIDATION

The mean modeling and simulation results were compared to the results of the BA studies. Figure 14 shows the predicted (in silico) and in vivo Cmax and AUC based on the Study PCR 1007. It should be noted similar overlay has been shown for the formulations used in other clinical studies (data not shown but can be found on pages 35-36).

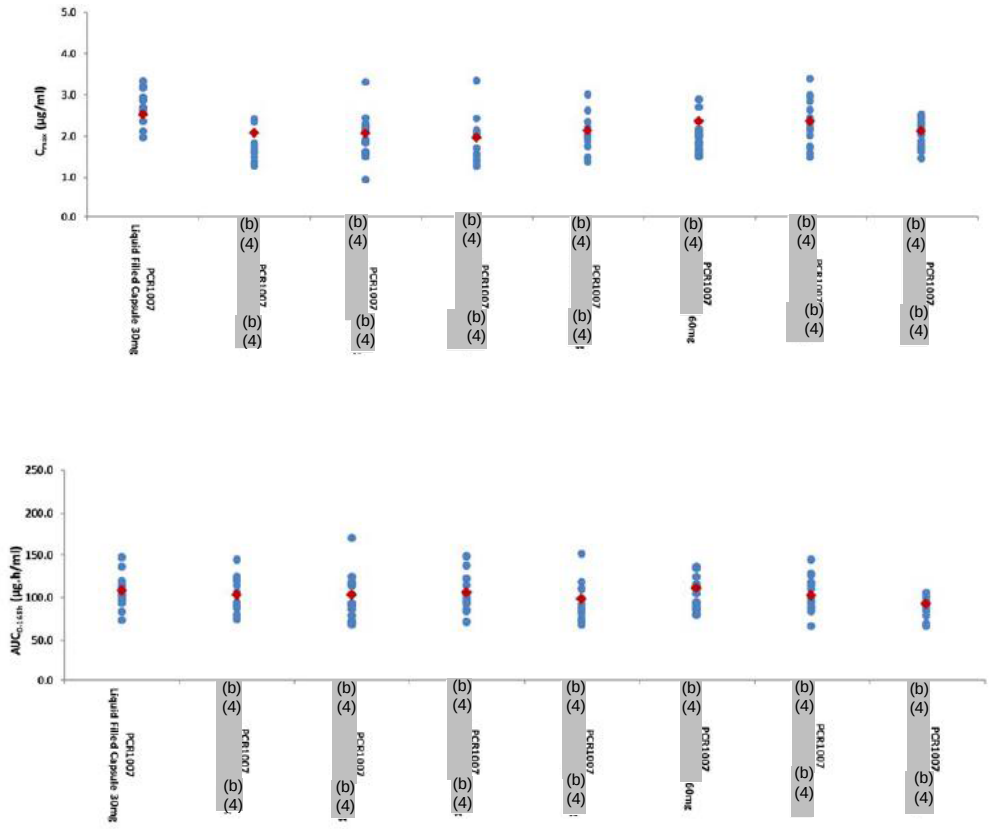

Figure 14. Individual Cmax (top panel) and AUC (bottom panel) values The in vivo data Study 1007 (blue) versus predicted in silico (red)

4. POPULATION SIMULATION

The Applicant conducted virtual trial population simulations. The Applicant included variability (%CV) for each parameter either based on the default values of the program, or on the knowledge from the results of the clinical studies. The results of the virtual simulation and the observed mean data are shown in Table 9. PBPK predicted concentration time profile and the observed PK profile from the fasting Study PCR1011 is shown in Figure 15.

Table 9. Overview of the virtual trial simulations and the ration of the in silico results with the in vivo observed data

Study	Formulation	Dose	C_{max} (µg/ml)					AUC_{last} (µg.h/ml)				
			in vivo		*in silico*		ratio	*in vivo*		*in silico*		ratio
			mean	stdev	mean	stdev		mean	stdev	mean	stdev	
PCR1007	Liquid Filled Capsule 30mg (b) (4)	240mg	2.73	0.38	2.59	0.37	0.95	107.30	18.63	110.03	23.88	1.03
PCR1007		240mg	1.75	0.37	2.06	0.25	1.18	103.00	20.74	102.32	17.25	0.99
PCR1007		240mg	1.94	0.54	1.91	0.32	0.98	99.89	26.46	95.50	20.65	0.96
PCR1007		240mg	1.88	0.54	1.94	0.18	1.03	102.38	22.87	103.51	18.41	1.01
PCR1007		240mg	2.01	0.43	2.12	0.29	1.05	92.86	22.80	99.85	26.18	1.08
PCR1007		240mg	1.97	0.41	2.34	0.33	1.19	102.99	18.81	113.60	29.76	1.10
PCR1007		240mg	2.30	0.58	2.36	0.19	1.03	105.40	20.10	105.13	30.13	1.00
PCR1007		240mg	2.04	0.35	2.25	0.18	1.10	88.22	12.35	97.66	26.93	1.11
PCR1011		240mg	2.70	0.49	2.33	0.23	0.86	98.64	14.03	96.79	21.11	0.98
PCR1011		240mg	2.58	0.46	2.57	0.40	1.00	109.60	15.13	108.36	22.21	0.99
PCR1011		240mg	2.42	0.38	2.42	0.32	1.00	120.48	25.72	107.40	25.71	0.89
PCR1011		240mg	2.05	0.41	2.03	0.33	0.99	107.77	22.83	101.60	19.54	0.94
PCR1011		240mg	2.36	0.72	2.35	0.38	1.00	117.98	31.34	104.29	19.66	0.88
PCR1015		60mg	0.593	0.096	0.555	0.043	0.94	26.55	4.25	24.23	5.65	0.91
PCR1015		60mg	0.573	0.107	0.564	0.077	0.98	29.47	4.01	24.87	6.61	0.84
PCR1015		60mg	0.615	0.109	0.596	0.092	0.97	27.25	4.21	25.96	7.72	0.95
PCR1015		60mg	0.620	0.104	0.588	0.078	0.95	27.86	4.83	25.29	6.39	0.91
PCR1015		60mg	0.668	0.081	0.643	0.104	0.96	29.56	5.19	28.11	4.96	0.95
PCR1017		60mg	0.633	0.123	0.595	0.075	0.94	26.60	5.77	25.89	5.80	0.97
PCR1017		60mg	0.628	0.143	0.603	0.058	0.96	26.54	5.19	26.70	6.73	1.01
PCR1017		60mg	0.614	0.133	0.614	0.091	1.00	26.16	5.05	25.66	7.16	0.98

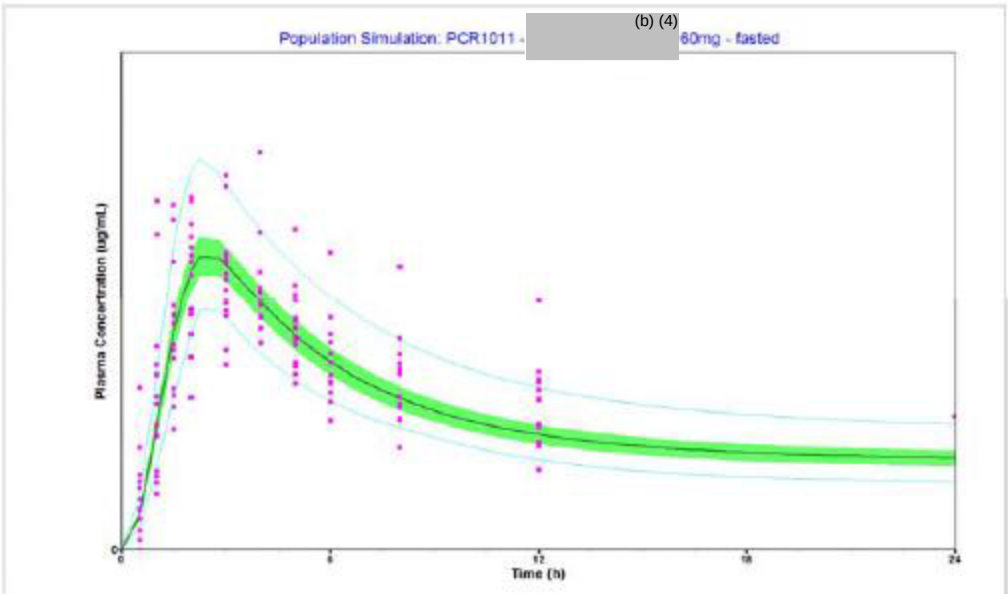

Figure 15. PBPK predicted (green) concentration time profile with the 95% probability plots (blue dash lines) as compared to the observed (pink squares) concentration vs time data of the proposed drug product

5. EVALUATION OF THE IMPACT OF THE PRESENCE OF (b) (4) (b) (4)

The Applicant utilized the mechanistic absorption model to evaluate the presence of different (b) (4) amounts in the drug product on the bioavailability. The Applicant utilized the (b) (4) collected after the administration of different levels of (b) (4) (b) (4) in the (b) (4) apalutamide formulation. The following framework was developed (Figure 16):

a. (b) (4) bioavailability study
b. Characterization of the PBDT dissolution profiles of the (b) (4) (b) (4)
c. (b) (4) mechanistic model of absorption
d. Two-Step Solubility approach for solubility input (b) (4)
e. Virtual BE trials: Virtual BE trials were performed to evaluate the exposure between drug product containing (b) (4) with the drug product containing different amounts of (b) (4) material

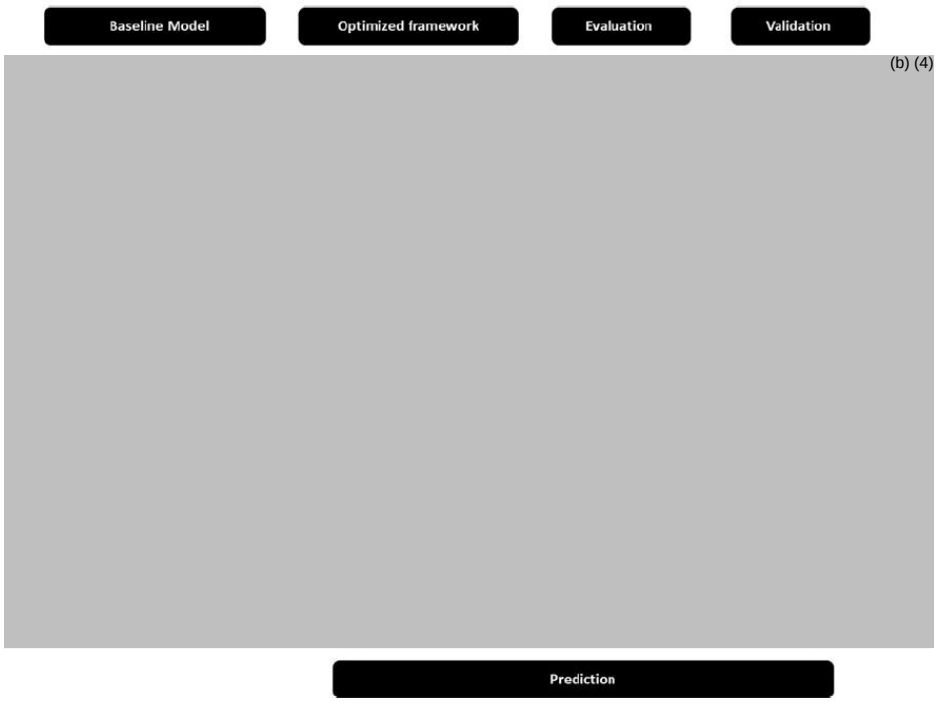

Figure 16. Overview of the absorption model to evaluate the impact of the presence of (b) (4) (b) (4).

A. (b) (4) BIOAVAILABILITY STUDY

Relative bioavailability of apalutamide formulations was also evaluated in (b) (4) . The absolute bioavailability (b) (4) were also 100% similar absorption was observed in humans. Table 10 shows the results of (b) (4) PK data.

Table 10. (b) (4) PK results for different formulations of apalutamide

Oral administration in (b) (4)				
Parameter	**Liquid filled capsule**	(b) (4)		
C_{max} (µg/ml)	4.11 ± 0.66	3.90 ± 0.86	4.21 ± 0.16	2.63 ± 0.15
T_{max} (h)	1 – 2	0.5 – 1	1 – 2	1 – 2
AUC_{0-168h} (µg.h/ml)	157 ± 41.3	183 ± 52.9	190 ± 105	159 ± 50.8
F_{rel}	---	1.17	1.21	1.01

B. PBDT PROFILES OF FORMULATIONS TESTED IN (b) (4) BIOAVAILABILITY STUDY

Dissolution profiles of (b) (4) (b) (4) and apalutamide drug product using the PBDT method is shown in Figure 17. As discussed above solubility of (b) (4) (b) (4) is low which is also reflected in the PBDT dissolution profile below.

Figure 17. PBDT profiles of (b) (4) and (b) (4) (b) (4)

C. (b) (4) MECHANISTIC MODEL OF ABSORPTION

The Applicant utilized the (b) (4) PK data after administration of iv and oral formulations (b) (4) as well as the PBDT profiles to predict the plasma concentration time profiles of the formulations spiked with (b) (4) (b) (4) (Figure 18).

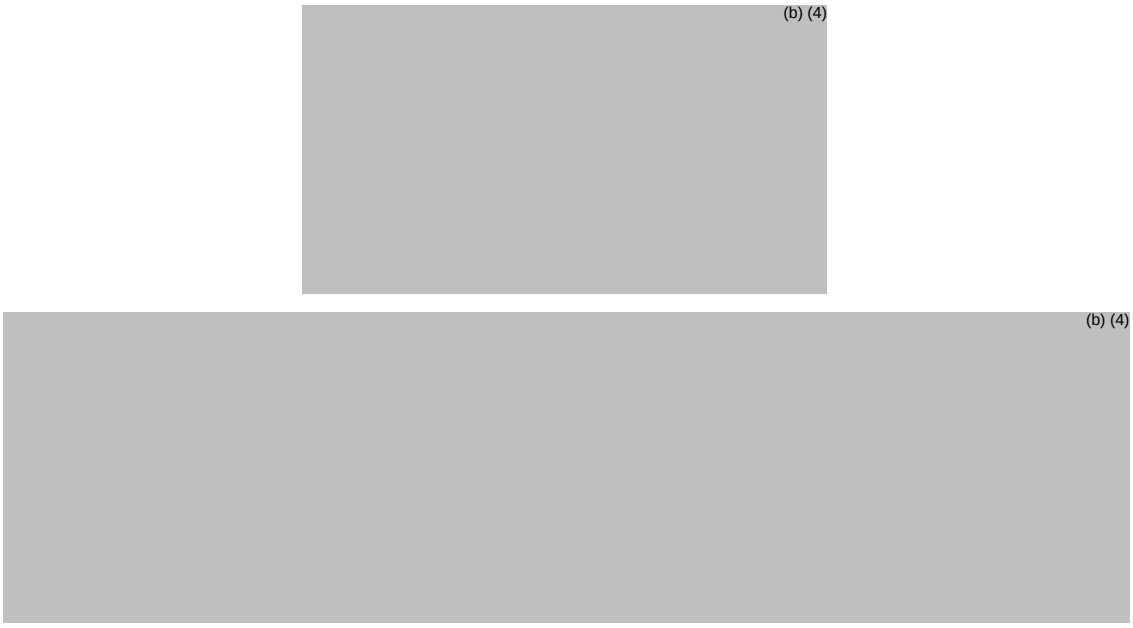

Figure 18. Predicted and observed concentration time profiles of apalutamide iv (top panel), (b) (4) oral administration (bottom left panel), and as (b) (4) (b) (4) (bottom right panel)

The mechanistic absorption model was able to predict the trends observed in (b) (4) study.

D. TWO-STEP SOLUBILITY APPROACH FOR SOLUBILITY INPUT FOR (b) (4)

The Applicant took an innovative approach to address the limitation of the Gastroplus modeling software when predicting the dissolution rates (b) (4) (b) (4)). The limitation of the model stems from the fact that (b) (4) for solubility for the drug substance cannot be entered. During the development of this model, the Applicant tried many other ways as shown in Table 11 below (PBDT input only, (b) (4)) to address this (b) (4) input issue, this approach resulted in better PK parameter and regional absorption parameter prediction.

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Figure 20 shows the predicted concentration time profiles after oral administration of (b) (4) (b) (4) containing different levels of (b) (4) (b) (4).

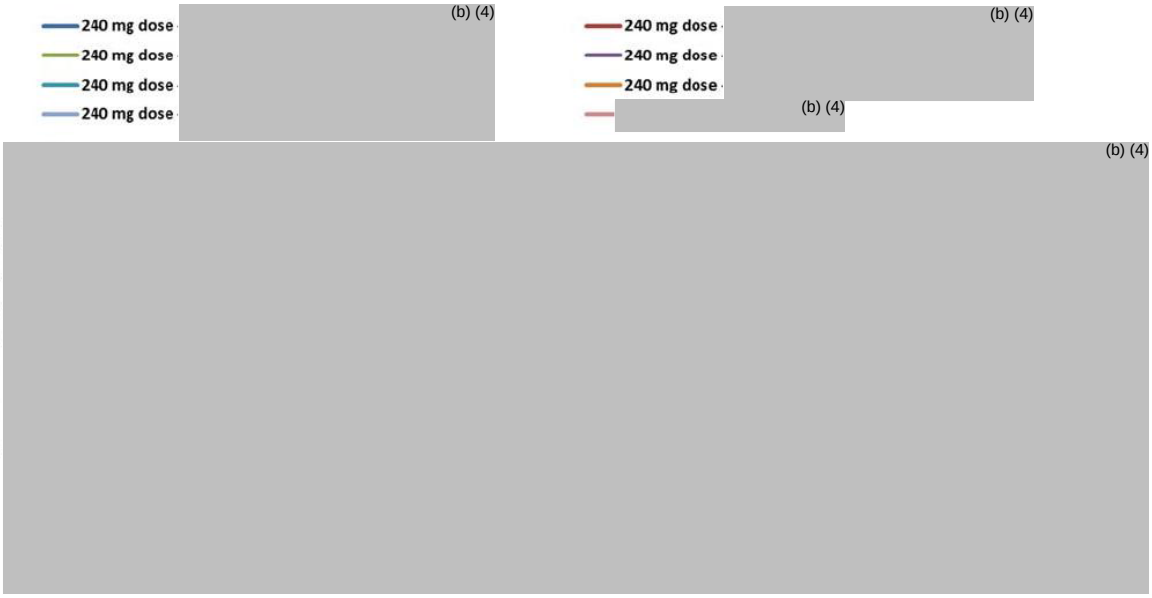

Figure 20. Simulation results (b) (4)

E. EVALUATION OF BIOEQUIVALENCE AND NON-BIOEQUIVALENCE: VIRTUAL BE TRIALS

The Applicant ran a virtual cross over trial to predict the bioequivalence of each of the formulations with different levels of (b) (4) (b) (4) The Applicant (b) (4) ran the virtual BE trials using Pharsight Phoenix. The results show that even at (b) (4) % (b) (4) the formulations are bioequivalent to the (b) (4) formulation (Table 12).

Table 12. Overview of the 90% CI's for predicted PK parameters after multiple BE trials

Virtual Trial Number	Virtual bioequivalence trials (Reference = apalutamide (b) (4) (b) (4)															
	C_{max}		$AUC_{0\text{-}168h}$		C_{max}		$AUC_{0\text{-}168h}$		C_{max}		$AUC_{0\text{-}168h}$		C_{max}		$AUC_{0\text{-}168h}$	
	90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI	
	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL
1	94.18	102.75	92.98	95.87	88.19	96.22	90.40	93.21	82.21	89.69	87.67	90.40	76.85	83.85	84.60	87.23
2	88.01	95.64	92.69	96.11	81.54	88.60	90.69	94.04	83.25	90.46	87.31	90.53	79.07	85.92	84.28	87.39
3	89.34	97.77	93.15	96.53	85.23	93.26	91.04	94.35	81.25	88.91	87.17	90.33	79.44	86.93	84.66	87.73
4	87.73	95.38	92.36	95.45	84.30	91.65	90.60	93.63	81.87	89.01	86.85	89.75	78.47	85.31	84.28	87.10
5	86.62	94.87	93.63	97.10	80.79	88.49	90.73	94.09	81.75	89.55	87.49	90.73	78.46	85.94	83.52	86.61
6	88.21	95.80	92.78	95.55	86.12	93.54	91.62	94.36	81.70	88.74	87.72	90.34	79.78	86.64	84.97	87.50
7	90.38	97.59	93.66	96.99	86.32	93.21	89.39	92.57	80.08	86.46	87.93	91.06	76.16	82.24	83.86	86.84
8	86.65	94.31	92.69	95.67	83.01	90.36	91.29	94.23	84.16	91.61	88.09	90.92	79.34	86.36	84.66	87.38
9	88.68	96.05	93.89	96.92	81.52	88.30	90.62	93.54	81.30	88.05	87.38	90.20	77.78	84.24	84.55	87.28
10	87.56	95.99	93.33	96.42	83.67	91.73	89.91	92.88	82.35	90.28	86.44	89.29	76.16	83.50	84.29	87.08

REVIEWER'S ASSESSMENT

The proposed dissolution method and acceptance criterion are acceptable. The dissolution method is able to discriminate the presence of (b) (4) material beyond (b) (4)%, and the dissolution method is over discriminatory for the selected range of (b) (4) particle size ((b) (4)).

It is important to recognize that mechanistic absorption modeling is now being utilized as an important tool to support selection of clinically relevant specifications. This review includes the overview of this model. The Applicant's mechanistic absorption model serves as a supportive data to show that up to (b) (4)% (b) (4) (b) (4) in the drug products were bioequivalent to each other. Since the Applicant controls the (b) (4) in the (b) (4) drug product, there are no potential risks that the (b) (4) material will exceed this level.

- ***BRIDGING OF FORMULATIONS***

Clinical development started with the 30-mg liquid filled capsule formulation. The Applicant changed the tablet dosage form which is the to-be-marketed formulation because of the stability issues and higher capsule pill burden observed with the capsules. During the clinical studies (Phase1/2, and Phase 1: Studies -001, 1008, 1010 and Phase 3: Spartan Study 003), the subject received tablet formulations as well as the capsule formulations. The Phase 1 hepatic impairment, cardiac and drug interaction studies (Study #1018, 1019, 1020, and 1021) were only conducted with the tablet formulation: The Applicant conducted a relative BE study (Study 1011) between the capsule and tablet formulation. Therefore, an adequate bridging exists between the clinical and the proposed commercial formulations.

- ***BIOWAIVER REQUEST***

Biowaiver request is not needed since there is only one strength of the proposed drug product. The Applicant characterized the PK profile of the proposed drug product.

APPENDIX 1.

Table 2: Composition of the 60 mg FC Tablet (G023)

Component	Quality Reference[a]	Function	Quantity per Tablet	
			(mg)	(% w/w)
Core Tablet				
(b) (4)				
Film Coat				
(b) (4)				
Total Weight:			721.00	

(b) (4)

(b) (4)

(b) (4)

APPENDIX 2

Study Design of PCR1007 Relative BA study

Treatment Arm	Platform	Dose strength
A	Liquid filled capsule	30 mg
B	(b) (4)	(b) (4)
C		
D		60 mg
E		(b) (4)
F		
G		
H		

Study Design of PCR1011 Relative BA study

Treatment Arm	Platform	Dose strength
A	Liquid filled capsule	30 mg
B	(b) (4)	60 mg
C		(b) (4)
D		
E*		60 mg

* food effect evaluation

Study Design of PCR1015 Crossover study

Treatment Arm	Formulation	Dose strength	Particle size (d50)
A	(b) (4)	60 mg	(b) (4)
B		60 mg	
C		60 mg	
D		60 mg	
E		60 mg	

Study Design of PCR1017 Crossover study

Treatment Arm	Formulation	Dose strength	(b) (4)
A	(b) (4)	60 mg	
B		60 mg	
C		60 mg	

Banu Zolnik

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ENVIRONMENTAL

IQA Review Guide Reference

R Regional Information

Summary: The applicant submitted a claim for a categorical exclusion for apalutamide from the requirement to prepare an environmental assessment (EA), per 21 CFR 25.31(b). The required statement of no knowledge of extraordinary circumstances was submitted, per 21 CFR 25.15(a). FDA requested additional information to support the claim. Based on a review of the information provided by the applicant, and additional information obtained by FDA, the claim for a categorical exclusion from an EA is acceptable.

Environmental

The applicant submitted a claim for a categorical exclusion for apalutamide from the requirement to prepare an environmental assessment (EA), per 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but where the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb, or µg/L). The expected introduction concentration (EIC) provided (b) (4) ppb. A statement was provided stating that to the applicant's knowledge, no extraordinary circumstances exist, which is required per 21 CFR 25.15(a) for whether such circumstances might significantly affect the quality of the human environment. FDA responded that it needed additional data to assist with reviewing the claim due to the relevance of apalutamide, an anti-androgen, to substances described in FDA's guidance for substances with the potential for hormonal effects in the environment (USFDA, 2016). In particular, while the EIC of (b) (4) µg/L will be less than the 1 µg/L exclusion level, a predicted no-effects concentration (PNEC) of less than (b) (4) µg/L appears possible based on another anti-androgen, cyproterone acetate (Kiparissis et al., 2003). While the expected environmental concentration (EEC) would be lower than the EIC due to metabolism, dilution, degradation, and other factors, thus lowering the likelihood of exceeding the PNEC, this would be offset by the uncertainties from the limited toxicity data set, reported insensitivity of current assays (e.g., OECD 230) to anti-androgens, and the potential for cumulative effects across all anti-androgens. Therefore, FDA requested that the applicant provide (1) available information for determining a more realistic EEC (e.g., metabolism and environmental degradation data); (2) available information for assessing environmental effects for this or similar substances (e.g., aquatic toxicity assay data, "read across" results); and (3) any other available information relevant to assessing the environmental impact of this substance (e.g., environmental risk assessments, fish plasma model (FPM) results such as those conducted by Nallani et al., 2016).

The applicant responded to FDA's request with additional data to support their claim for an exclusion from an EA. Briefly, the data included a more realistic EEC based on estimate of metabolism for apalutamide of 25% and a dilution factor of 0.1. The

substance was not considered readily biodegradable. The result was an EEC of (b) (4) µg/L. The environmental effects of apalutamide in aquatic organisms were investigated in a battery of toxicity studies conducted according to OECD, with a lowest no-observed effects concentration (NOEC) of (b) (4) µg/L. Thus, the margin of exposure (MOE) is (b) (4) µg/L / (b) (4) µg/L = (b) (4) The applicant also applied an FPM to the EEC, with a resulting MOE of (b) (4), which is similar to FDA's FPM MOE of (b) (4). The FDA FPM used a more refined approach, but also a more conservative concentration, the EIC, which essentially cancelled each other out.

The applicant concluded that, based on multiple lines of evidence, no adverse environmental effects are anticipated as a consequence of the use of apalutamide for the treatment of prostate cancer.

References:

Kiparissis Y, Metcalfe TL, Balch GC, Metcalfe CD. 2003. Effects of the antiandrogens, vinclozolin and cyproterone acetate on gonadal development in the Japanese medaka (Oryzeias latipes). Aquat Toxicol 63, 391-403.

Nallani G, Venables B, Constantine L, Huggett D. 2016. Comparison of measured and predicted bioconcentration estimates of pharmaceuticals in fish plasma and prediction of chronic risk. Bulletin of Environmental Contamination and Toxicology, 96(5):580-584.

USFDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Biologics Evaluation and Research. US Food and Drug Administration, Silver Spring, MD. Available at https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf

Reviewer's Assessment:

The specific claim for a categorical exclusion for apalutamide under 21 CFR 25.31(b) is appropriate for the estimated concentrations. The required statement of no extraordinary circumstances, per 21 CFR 25.15(a), was included with the claim. FDA requested additional data to assist with reviewing the claim due to the relevance of apalutamide, an anti-androgen, to substances described in FDA's guidance for substances with the potential for hormonal effects in the environment (USFDA, 2016). The applicant responded to FDA's request with additional data to support their claim for an exclusion. FDA reviewed the supporting data and agreed based on the multiple lines of evidence presented by the applicant and the additional data obtained by FDA, no adverse environmental effects are anticipated as a consequence of approval of this application. The claim for a categorical exclusion from an EA is acceptable.

Primary Environmental Reviewer Name and Date: James Laurenson, January 25, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, January 26, 2017

James Laurenson

Digitally signed by James Laurenson
Date: 1/25/2018 10:52:34AM
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Michael Furness

Digitally signed by Michael Furness
Date: 1/26/2018 09:09:54AM
GUID: 502e8c7600003dd8331cf6eebf43697a

Risk Assessment Table NDA 210951

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	Controlled for in specifications.	L	None
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	(b) (4)	L	None
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled for in specifications.	L	None
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled for in specifications.	L	L
Dissolution – BCS Class (b) (4)	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M	Controlled for in specifications The method is discriminating for the presence of (b) (4) material (b) (4)	L	None

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Xiao Chen

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Date: 2/02/2018 11:36:07AM
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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 210951	**Established/Proper Name: Apalutamide**
Applicant: Janssen Pharmaceuticals Inc	**Dosage Form: Tablets**
Submission Type: 505b1	**Strength(s): 60 mg**
Chemical Type: Type 1	**Cross Referenced Applications: IND 104676**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			None.
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			None.

B. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

Apalutamide is a small molecule NME drug to be orally administered to patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC). The drug received fast track designation. The NDA was submitted through a rolling submission, and CMC portion was submitted on 9/29/2017. The PDUFA goal date for the NDA is 4/10/2018, and the target action date is 2/20/2018.

(b) (4) Apalutamide is a BCS class 2 compound with a low solubility in aqueous media. The DP is an IR 60 mg strength film coated tablet. The tablets are manufactured from a (b) (4) Twelve months long term stability data for the primary stability batches were submitted.

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	X			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	X			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	X			
	FACILITY INFORMATION				
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	X			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	X			
	DRUG SUBSTANCE INFORMATION				
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?			X	All in vivo clinical pharmacology studies will be assessed by OCP. However, the Applicant has submitted results of PBPK modeling and a virtual BE study to support a (b) (4) content of (b) (4)% in the drug product. The Division of Biopharmaceutics will assess the

C. FILING CONSIDERATIONS					
					PBPK model and decide on the maximum (b) (4) for the drug product. Biopharmaceutics will assess the dissolution method, for routine QC batch release and stability testing, for its suitability for the drug product.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	X			Although the 60 mg tablet formulation was used in the Phase 3 study, a bridging PK study was performed. The TBM tablet formulation (debossed) is bridged to the clinical 60 mg tablet by comparative dissolution data.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.		X		Approval is being sort for only one tablet film coated strength, 60 mg.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			X	The dosage form is an immediate release tablet.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?		X		The Applicant asserts that the drug substance is a BCS-2 compound.
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	X			
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?			X	
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			X	
17.	For Biotech Products, is sufficient information provided in compliance with 21 CFR 610.9 and 601.2(a)?			X	

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: **This process will be reviewed approximately 150 days from date issued (May 24, 2016).**
Version	**Summary of Changes** **Date Issued**
01	Initial 05/24/2016

Xiao Chen

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Date: 11/06/2017 03:49:57PM
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