CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210308Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210308
Review #1

Drug Name/Dosage Form	Abiraterone Acetate Tablet
Strength	125 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Churchill Pharmaceuticals LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	05/19/2017	API/DP/Process/Biopharm/Facility
Quality Amendment 0011	11/16/2017	API/DP/ Process
Quality Amendment 0013	01/05/2018	DP/ Process
Quality Amendment 0014	01/12/2018	Process
Quality Amendment 0015	01/19/2018	DP/Process
Quality Amendment 0016	01/22/2018	DP
Quality Amendment 0017	01/26/2018	Biopharm
Quality Amendment 0018	01/29/2018	DP
Quality Amendment 0019	02/02/2018	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gaetan Ladouceur	CDER/OPQ/ONDP/DNDAPI
Drug Product	Rajiv Agarwal	CDER/OPQ/ONDP/DNDP1
Process	Sung Kim/Maotang Zhou	CDER/OPQ/OPF/DPA1
Microbiology	N/A	
Facility	Zhong Li	CDER/OPQ/OPF/DIA
Biopharmaceutics	Yang Zhao	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	N/A	
Environmental	Rajiv Agarwal	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 III	[redacted]	(b) (4) [redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	NAdequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type III	[redacted]	[redacted]	Adequate	No DMF review is needed.	Adequate info in the NDA
[redacted]	Type II	[redacted]	[redacted]	Adequate	February 27, 2018	Reviewed by Dr. Ryan Holland
[redacted]	Type II	[redacted]	[redacted]	Adequate	October 10, 2017	Adequate info in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	115577	Initial IND was submitted on 2/21/2014

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 in NDA 210308 for Yonsa™ abiraterone acetate tablets has been reviewed 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 Yonsa™ abiraterone acetate 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].

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	YONSA is a CYP17 inhibitor indicated in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	Metastatic castration-resistant prostate cancer: YONSA 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally **twice** daily.
• **Alternative Methods of Administration**	N/A

B. Quality Assessment Overview

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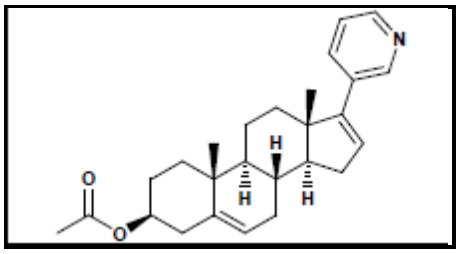
Drug substance

- Chemical Name and Structure:

Name: Abiraterone Acetate

Chemical Name: (3beta)-17-(3-pyridinyl)-Androsta-5,16-dien-3-ol acetate (ester); Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-acetate (ester), (3β); 17-(Pyridin-3-yl)androsta-5,16-dien-3β-yl acetate

Structure:



Molecular Weight: 391.54

The drug substance is a white crystalline powder. It has a melting temperature of 127-130oC. It is very soluble in dichloromethane, freely soluble in dioxane, soluble in ethanol, ethyl acetate and acetone and practically insoluble in water. The product is not hygroscopic.

Full CMC information for Abiraterone Acetate is provided in DMF (b) (4). DMF (b) (4) has been reviewed by Dr. Ryan Holland and found to be adequate. Refer to his review dated February 27, 2018 in Panorama.

Drug product

The drug product is a white to off white oval shaped immediate release tablet debossed with "125 FP" containing 125 mg of Abiraterone acetate. Only compendial excipients common for oral formulations are used for the manufacture of Yonsa tablet. 120 (commercial) and 28 (Physician sample) counts tablets are packaged in HDPE (b) (4) bottles and closed with child resistant lined closures. (b) (4)

Per ICH Q3D, applicant provides a complete risk assessment on 2-MAR-2018 (SDN23). Risk assessment demonstrates that the levels of Class 1 and Class 2A elements are adequately controlled in the active pharmaceutical ingredient and all excipients. The levels of (b) (4) respectively, are also adequately controlled. Finally, the elemental components of (b) (4) are adequately controlled during the manufacturing process for (b) (4). None of the elements of concern are expected to be present in YONSA at levels that would result in daily exposures exceeding the Permitted Daily Exposure limits at the recommended YONSA dose of four tablets daily. Based on the data, the total elemental impurity level from all sources in the drug product is expected to be consistently less than (b) (4) percent of the PDE and therefore additional controls are not required.

The stability of the drug product was studied using the proposed commercial excipients in the formulated drug product in accordance with the ICH 1A and Q1B. The stability studies demonstrate that excipients are compatible at the concentrations used in the drug product formulation. The stability assessment for Yonsa/125 mg tablets is currently based on the study results of 24-months data for three commercial scale batches stored at 25°C/60 % RH and 6-months data for the same batches stored at 40°C/75 % RH.

Based on the 24-months of stability data (see table in section P.8 under Reviewer's Assessment) on most batches and 28-months data on one batch packaged in (b) (4) bottle, generated on Abiraterone acetate for tablet registration stability batches, Churchill proposed a (b) (4) months of the expiration dating period.

Based on the real time data, it may be predicted that at (b) (4) month time, the (b) (4) degradation product may result in Out of Specifications results, therefore, it is determined that only **24** months of expiration period dating may be grated for the product packaged in (b) (4) HDPE (b) (4) bottle. The applicant accepts the proposal via amendment dated 5-JAN-2018.

Drug Product Manufacturing Process

Manufacturing process consists of (b) (4)

(b) (4)

Facility

Based on compliance history review and considering the proposed manufacturing to be conducted at each of the sites, the Drug Substance (FEI# (b) (4)) and Drug Product (FEI# (b) (4), FEI# (b) (4)) 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 Biopharmaceutics Review focuses on the evaluation of the adequacy of the proposed dissolution method and acceptance criterion for routine QC testing of the proposed drug product at batch release and during stability. The following Applicant's proposed dissolution method and dissolution acceptance criterion are acceptable for batch release and stability testing of the proposed Abiraterone acetate Tablets, 125 mg.

Acceptable dissolution method and acceptance criterion for YONSA™ (Abiraterone acetate) Tablets 125 mg				
USP Apparatus	**Speed (rpms)**	**Medium/Temp**	**Volume (mL)**	**Acceptance Criterion**

II (paddle)	75	pH 4.5 phosphate buffer with 0.12% sodium lauryl sulfate (SLS) @ 37±0.5 °C	900	Q = (b) (4) % dissolved in 15 minutes

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.

5-Mar-2018

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LABELING

R Regional Information

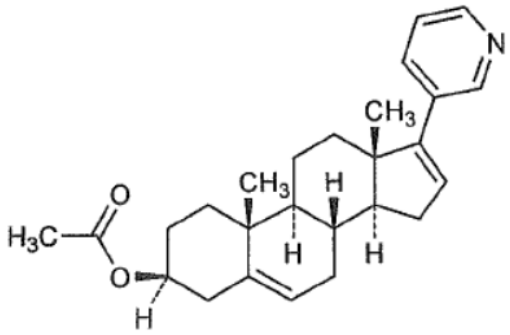
1.14 Labeling

Labeling & Package Insert

DESCRIPTION section:

11 DESCRIPTION

Abiraterone acetate, the active ingredient of YONSA tablet is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each YONSA Tablet contains 125 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is micronized (smaller particle size) (b) (4) white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, sodium stearyl fumarate, butylated hydroxyanisole, butylated hydroxytoluene.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

YONSA (abiraterone acetate) tablets, 125 mg (b) (4) white to off-white, oval-shaped tablets debossed with "125 FP" on one side. (b) (4) tablets are available in high-density polyethylene (b) (4) bottles (b) (4)

(b) (4)

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Women who are pregnant or women who may be pregnant should not handle YONSA without protection, e.g., gloves *[see Use in Specific Populations (8.1)]*.

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of YONSA is 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. YONSA tablets can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole with water. Do not crush or chew tablets.

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?

☒ Yes ☐ No ☐ N/A

If "No," explain.

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(b) (4)

Reviewer's Assessment: *The applicant responsed to deficiencies and revised the label as recommended. Adequate.*

Reviewer's Assessment:

The labeling of the PI and container labels is revised per lebelling tools and https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM569607.pdf *guidance to have the most current information of the labels.*

The deficiencies were identified and communicated to the applicant by DMEPA in collaborations with OPPQ/OPQ and ONDP. The applicant responded satisfactorily on 29-JAN-2018 to the deficiencies identified for container closures.

The container labeling and PI is now adequate. A final version of the agreed upon PI will be reviewed by the ATL and included in their memo.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 30-JAN-2018

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

Anamitro Banerjee, PhD,

Rajiv Agarwal

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Date: 2/09/2018 03:26:37PM
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Anamitro Banerjee

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Date: 2/09/2018 06:52:00PM
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BIOPHARMACEUTICS

NDA: 210308-ORIG-1

Drug Product Name/Strength: YONSA™ (abiraterone acetate) Tablets (b) (4)/125 mg

Route of Administration: Oral

Applicant Name: Churchill Pharmaceuticals

Product Background: Abiraterone is a CYP17 inhibitor, in combination with methylprednisolone, indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

The recommended dose of Abiraterone acetate Tablets, 125 mg, is 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. (b) (4) .

The Listed Drug (LD) is Zytiga™ (Abiraterone acetate) Tablets, 250 mg (NDA 202379), manufactured by Janssen Biotech and approved by FDA on 4/28/2011.

Review Recommendation: **Adequate**

Review Summary:

Submission: Churchill Pharmaceuticals submitted this NDA seeking approval for YONSA™ (Abiraterone acetate) Tablets 125 mg under section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act.

Review's Objective: The Biopharmaceutics Review focuses on the evaluation of the adequacy of the proposed dissolution method and acceptance criterion for routine QC testing of the proposed drug product at batch release and during stability.

Reviewer's Assessment: The following Applicant's proposed dissolution method and dissolution acceptance criterion are acceptable for batch release and stability testing of the proposed Abiraterone acetate Tablets, 125 mg.

Acceptable dissolution method and acceptance criterion for YONSA™ (Abiraterone acetate) Tablets 125 mg				
USP Apparatus	**Speed (rpms)**	**Medium/Temp**	**Volume (mL)**	**Acceptance Criterion**
II (paddle)	75	pH 4.5 phosphate buffer with 0.12% sodium lauryl sulfate (SLS) @ 37±0.5 °C	900	Q = (b) (4) % dissolved in 15 minutes

Recommendation: From the Biopharmaceutics perspective, NDA-210308 for YONSA™ (abiraterone acetate) Tablets 125 mg is recommended for **APPROVAL**.

List of submissions being reviewed (table):

Original NDA-210803 submitted on May 19, 2017
DMF- (b) (4)
Applicant's IR Response dated January 26, 2018 (to the Information Request dated January 16, 2018)

Highlight of key outstanding issues from last cycle: None; this is the first review cycle.

Concise description of outstanding issues: None

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: ADEQUATE

REVIEW:

1. **Pharmaceutical development of the proposed drug product and drug substance particle size distribution:**

(b) (4)

Table 1. Composition of SoluMatrix Abiraterone Acetate Tablets, 125 mg

Ingredient	Amount per tablet (mg/tablet weight)	Function	Quality Standard
Abiraterone acetate	125.00	Active pharmaceutical ingredient	See Section 3.2.S.4.1 Specifications
Lactose monohydrate	(b) (4)		NF
Sodium lauryl sulfate			NF
Butylated hydroxyanisole			NF
Butylated hydroxytoluene			NF
Microcrystalline cellulose			NF
Croscarmellose sodium			NF
Sodium stearyl fumarate			NF
Total	**870.0**		

Table 2. Summary of abiraterone acetate drug substance lots and uses

Manufacturer	Lot Number	Manufacturing Date	Batch use
(b) (4)	A1307A0103	16 Jul 2013	Phase 1 BA Dose Range study (CHL-AA-101)
	AB-006/14M	07 May 2014	Phase 1 Pivotal BE study (CHL-AA-102)
	AB-023/14M	18 Nov 2014	Phase 1 Food Effect study (CHL-AA-103) Phase 1 Drug Interaction study (CHL-AA-104) Phase 2 Patient studies (CHL-AA-201 and CHL-AA-202) Primary Stability Batch
	AB-024/14M	21 Nov 2014	Primary Stability Batch
	AB-025/14M	24 Nov 2014	Primary Stability Batch

Table 3. Particle size distribution for different abiraterone acetate drug substance lots

DS lot	D10, µm	D50, µm	D90, µm
A1307A0103	(b) (4)		
AB-006/14M			
AB-023/14M			
AB-024/14M			
AB-025/14M			

2. Solubility of abiraterone acetate:

In an IR Response dated January 26, 2018, the Applicant provided solubility data for abiraterone acetate (Table 4).

Table 4. Solubility of abiraterone acetate at room temperature

Media	Abiraterone Acetate Solubility at Ambient Temperature (mg/mL)
USP Hydrochloric Acid Buffer, pH 1.2	0.137
USP HCl buffer, pH 1.2 with 0.1% polysorbate 80	0.347
USP HCl buffer, pH 1.2 with 1% polysorbate 80	gel formed
USP HCL buffer, pH 1.2 with 0.1% CTAB	0.653
USP HCL buffer, pH 1.2 with 1% CTAB	> 2
0.01N HCl (pH 2)	0.004
0.01N HCl (pH 2) with 0.1% SLS	gel formed
0.01N HCl (pH 2) with 0.1% poloxamer 188	0.005
0.01N HCl (pH 2) with 0.5% polysorbate 80	0.180
0.01N HCl (pH 2) with 1% polysorbate 80	0.340
0.01N HCl (pH 2) with 1.5% polysorbate 80	0.514
0.01N HCl (pH 2) with 2% polysorbate 80	0.621
0.01N HCl (pH 2) with 4% polysorbate 80	> 1
USP acid phthalate buffer, pH 3.0 with 0.1% polysorbate 80	0.038
USP acid phthalate buffer, pH 3.0 with 1% polysorbate 80	0.355
USP acid phthalate buffer, pH 3.0 with 0.1% CTAB	0.058
USP acid phthalate buffer, pH 3.0 with 1% CTAB	High viscosity/ not tested
56.5mM Phosphate Buffer pH 4.5	<0.005
56.5mM Phosphate Buffer pH 4.5 with 0.025%SLS	0.006
56.5mM Phosphate Buffer pH 4.5 with 0.05%SLS	0.131
56.5mM Phosphate Buffer pH 4.5 with 0.10%SLS	0.373
56.5mM Phosphate Buffer pH 4.5 with 0.12%SLS	0.535
56.5mM Phosphate Buffer pH 4.5 with 0.1% polysorbate 80	0.008
56.5mM Phosphate Buffer pH 4.5 with 1% polysorbate 80	0.083
56.5mM Phosphate Buffer pH 4.5 with 0.1% CTAB	0.068
56.5mM Phosphate Buffer pH 4.5 with 1% CTAB	0.554
Phosphate Buffer pH 6.8	Not detected
Phosphate Buffer pH 6.8 with 0.1% SLS	<quantitation limit
Phosphate Buffer pH 6.8 with 0.25% SLS	0.244
Phosphate Buffer pH 6.8 with 0.5% SLS	0.518
Phosphate Buffer pH 6.8 with 0.75% SLS	0.792
Phosphate Buffer pH 6.8 with 1% SLS	0.970
Phosphate Buffer pH 6.8 with 2% SLS	>1
USP Phosphate buffer, pH 7.8	Not detected

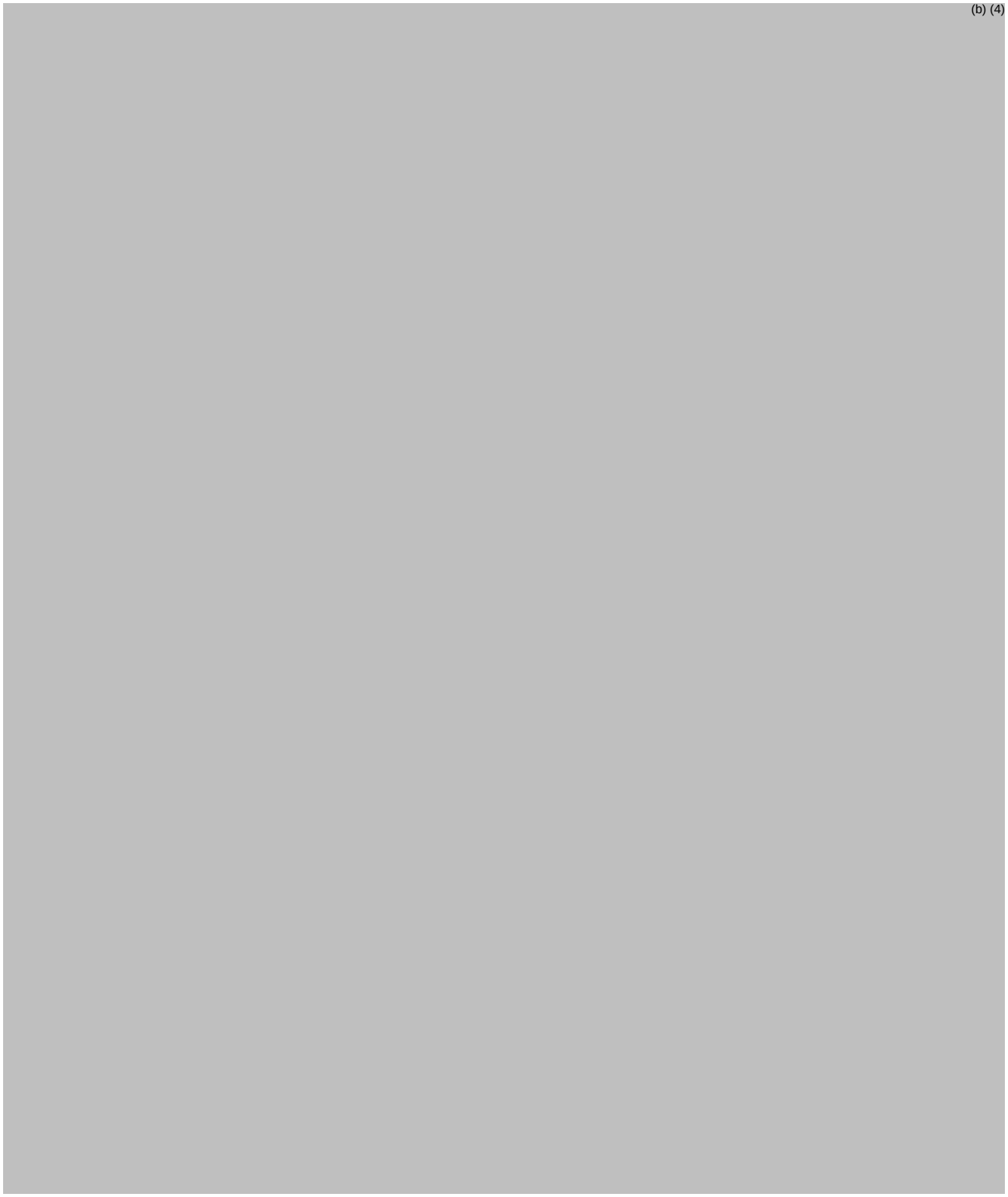
Abbreviation: CTAB = cetyl trimethylammonium bromide, SLS = sodium lauryl sulfate

3. Proposed dissolution method and dissolution acceptance criterion:

The proposed dissolution method and dissolution acceptance criterion for Abiraterone acetate Tablets, 125 mg, are as follows:

Apparatus: USP apparatus II (Paddle)
Paddle Speed: 75 rpm
Medium: pH 4.5 phosphate buffer with 0.12% SLS
Volume: 900 mL
Temperature: 37 ºC
Dissolution acceptance criterion: Q = (b) (4) % dissolved in 15 minutes.

(b) (4)



(4) Dissolution data obtained using the proposed dissolution method: The Applicant provided the dissolution profiles of the proposed SAA Tablets and LD using the proposed dissolution method (USP II at 75 rpm, 900 mL of 0.12% SLS pH 4.5 medium at 37 °C) (Figure 8 and Table 6).

Figure 8. Comparative dissolution profiles for SAA Tablets, 125 mg and LD using the proposed dissolution method

Time (min)	% Released (n=6)			
	SAA Tablets Batch 140724-CH-1		Zytiga Lot SSDD (1/2 tablet per vessel)	
	Mean	%RSD	Mean	%RSD
2	26.9	10.0	19.3	8.1
4	52.3	12.1	29.0	7.6
6	72.4	7.9	38.3	6.3
8	88.1	3.1	47.5	5.6
10	92.3	2.0	58.0	5.5
12	93.5	1.9	67.5	3.8
14	94.0	1.5	74.5	3.8
16	94.7	1.4	80.8	2.6
18	95.1	1.8	85.3	2.0
20	95.3	1.8	94.0	1.5
30	95.7	1.0	96.3	1.1
60	95.9	1.3	8.6	11.2

F2 = **24.5** (note: calculation based on 1st 10 timepoints, using n=6)

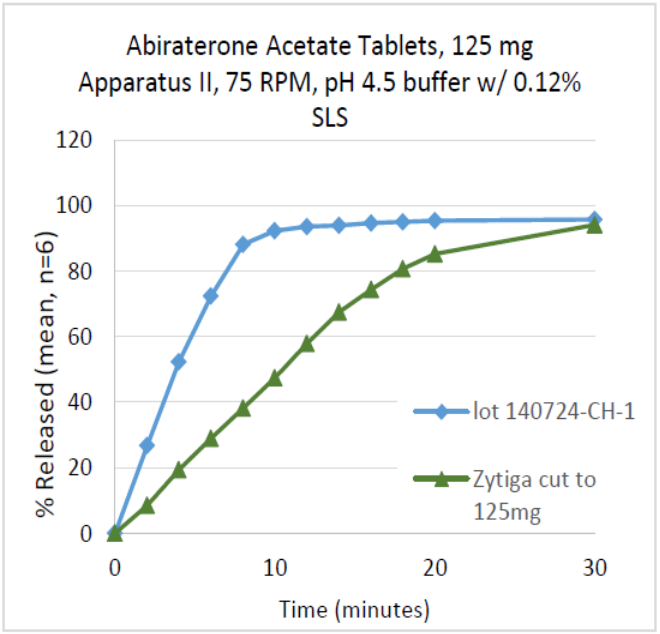


Table 6. Dissolution profile data for SoluMatrix Abiraterone Acetate Tablets, 125 mg clinical and commercial batches (Page 8, 'Summary of Biopharmaceutical Studies') (see Table 9 for more batch information)

% Released (average of n= 6)												
Batch Number	Phase 1[a] 13M256		Phase 1[b] 14J102		Phase 1 and 2[c] 15A003		Primary Stability 15A004		Primary Stability 15A005		Commercial Scale Batch 15/119-106	
Batch Size	(b) (4)											
Dose	100 mg		125 mg		125 mg		125 mg		125 mg		125 mg	
Time (min)	Mean	%RSD	Mean	%RSD	Mean	%RSD	Mean	%RSD	Mean	%RSD	Mean	%RSD
5	88	7.2	53	6.6	43	9.6	45	7.4	44	7.8	46	4.1
10	99	1.8	86	3.4	76	7.3	82	7.0	77	8.4	84	4.4
15	99	1.1	93	3.5	90	0.9	94	1.9	96	2.2	95	2.5
30	100	1.1	95	2.9	92	2.1	96	1.6	100	1.4	95	2.6
45	100	1.2	95	3.1	93	1.8	97	2.1	100	1.5	95	2.5
60	100	1.2	95	3.0	93	1.8	96	1.6	100	1.7	96	3.0

[a] CHL-AA-101

[b] CHL-AA-102

[c] CHL-AA-103, CHL-AA-104, CHL-AA-201, CHL-AA-202 this batch was also used as Primary Stability Batch

Reviewer's Assessment: The Applicant's proposed dissolution testing conditions (*USP II at* (b) (4) *rpm, 900 mL of 0.12% SLS pH 4.5 medium at 37 °C*) are acceptable for batch release and stability testing of Abiraterone Acetate Tablets, 125 mg.

In addition, based on the provided dissolution data, the proposed dissolution acceptance criterion of "Q (b) (4)% in 15 minutes" is acceptable.

4. Discriminating ability of the propose dissolution method:

The Applicant provided the data for investigating discriminating ability of the proposed dissolution method.

(b) (4)

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Reviewer's Assessment: Though the Applicant asserts that the proposed dissolution method is discriminating for (b) (4) particle size, in view of the variation in the dissolution data and borderline f_2 values, this Reviewer considered the discriminating ability of the dissolution method for (b) (4) particle size as inconclusive. Considering that the proposed drug product is immediate-release and (b) (4) in the dissolution medium is likely to generate incomplete dissolution, this Reviewer considered the proposed dissolution method acceptable for the QC dissolution method for Abiraterone Acetate Tablets, 125 mg.

5. Dissolution stability data:

The Applicant provided 12 and 24 months long term (25 °C/60% RH) and 6 months accelerated (40 °C/75% RH) stability data for different batches packed in different configurations (28-count bottle, 120-count bottle, HDPE bottles (b) (4) (Table 8).

The stability dissolution data indicate that these batches meet the proposed dissolution acceptance criterion of Q = (b) (4)% in 15 minutes. The proposed drug product is stable with regards to dissolution for at least 24 months under long term storage conditions.

Table 8. Dissolution data at 15 minutes of long term stability samples for the proposed SoluMatrix Abiraterone Acetate Tablets, 125 mg

	0 months	3 months	6 months	12 months	24 months
(b) (4)					

Bridging of Formulations

Reviewer's Assessment: ADEQUATE

Clinical studies were conducted using two different tablet formulations (Table 9). The formulations were (b) (4), with the primary difference (b) (4) The Phase 1 BA Dose Ranging study (CHL-AA-101) was conducted using the Proof of Concept (POC) formulation.

The dissolution tests for the commercial formulation used in Phase 1 (CHL-AA-102, CHL-AA-103 and CHL-AA-104) and Phase 2 (CHL-AA-201 and CHL-AA-202) clinical trials were conducted using the above proposed dissolution method (b) (4) And the dissolution tests for the POC formulation (CHL-AA-101 used in Phase 1 BA dose ranging clinical trial) were conducted using USP Apparatus II (paddle) at 75 rpm in 900 mL of pH 4.5 phosphate buffer with 0.1% SLS dissolution medium at 37 °C (b) (4)). The dissolution profiles for different SoluMatrix Abiraterone Acetate Tablets clinical and commercial batches are similar with more than (b) (4) % drug released in 15 minutes (Table 6).

Table 9. Different clinical batch formulations for the proposed SoluMatrix Abiraterone Acetate Tablets, 125 mg

Use	CHL-AA-101[a]	CHL-AA-102[b]	CHL-AA-103, CHL-AA-104 CHL-AA-201, CHL-AA-202[c]
Formulation	Proof of Concept	Commercial	Commercial
Tablet Strength	100 mg	125 mg	125 mg
(b) (4)			

[a] Phase 1 BA Dose Range Study
[b] Phase 1 Pivotal BE Study
[c] Phase 1 Food Effect, Phase 1 Drug Interaction and Phase 2 Patient Studies

REVIEWER'S OVERALL ASSESSMENT:

Dissolution Method: Though the proposed dissolution method did not demonstrate robust discriminating ability, the proposed dissolution method (USP apparatus II at 75 rpm, 900 mL of pH 4.5 phosphate buffer with 0.12% SLS) for the quality control of the proposed immediate release SoluMatrix Abiraterone Acetate Tablets, 125 mg, is **acceptable.**

Acceptance Criterion: The proposed dissolution acceptance criterion of "Q= (b) (4) % drug dissolved in 15 minutes" for the proposed SoluMatrix Abiraterone Acetate Tablets 125 mg is **acceptable**.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

Biowaiver Request

Reviewer's Assessment: N/A

List of Deficiencies: None

Primary Biopharmaceutics Reviewer: Yang Zhao, Ph.D. 2/6/2018

Secondary Biopharmaceutics Reviewer: Okpo Eradiri, Ph.D. 2/12/2018

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Yang Zhao

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Okponanabofa Eradiri

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

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 (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	H	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution– BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	H	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval

b)

Rajiv Agarwal

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