CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203415Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 203-415, XTANDI (enzalutamide) Capsules, 40 mg
Date: 29-AUG-2012

Introduction

XTANDI (enzalutamide) Capsules are formulated as opaque liquid-filled and imprinted soft gelatin capsules. Each capsule contains 40 mg of enzalutamide in a solution of caprylocaproyl polyoxylglycerides, NF. Butylated hydroxyanisole, NF and butylated hydroxytoluene, NF are also included as antioxidants in the formulation.

Enzalutamide is an androgen receptor signaling inhibitor indicated for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4). The recommended daily dose is four capsules, taken orally, taken with or without food.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 20-JUN-2012.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA.

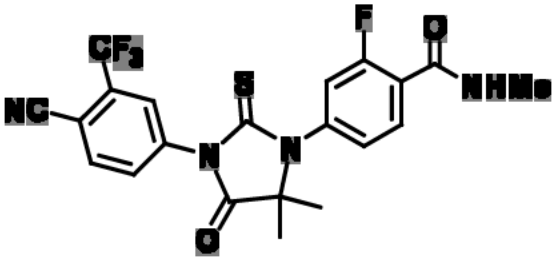
Administrative

The original submission of this 505(b)(1) NDA was received on 22-MAY-2012. Several solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (for the Drug Substance, 22-AUG-2012 by Dr. G. Ladouceur), Chemistry Review #1 (for the Drug Product, 22-AUG-2012 by Dr. D. Ghosh) and the Biopharmaceutics Review (15-AUG-2012, Dr. D. Lakhani).

The NDA is supported by IND 74,563 and nine (9) drug master files (DMFs). All DMFs were assessed for adequacy in the respective chemistry reviews.

Drug Substance (enzalutamide)

Chemical Name: 4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide



Molecular Formula $C_{21}H_{16}N_4O_2S$
Molecular Weight 464.4 g/mol

Enzalutamide is a new molecular entity. It possesses [redacted] and is manufactured as [redacted]. It is not hygroscopic and is practically insoluble in aqueous solutions.

The Applicant employs a [redacted] step [redacted] for the drug substance. This strategy was not altered during development. The Applicant identified and proposed Critical Process Parameters as part of the CMC dossier. During the review, the Applicant was asked to provide additional detail regarding the manufacturing process description. The Applicant was also asked to incorporate testing and acceptance criteria for impurities in a starting material [redacted], to provide some omitted batch analysis, and to supply missing Certificates of Analysis in support of the utilized reference standard. The Applicant's collective responses satisfactorily resolved these deficiencies.

Enzalutamide is relatively stable; no extraordinary storage precautions are required. The proposed **re-test period of** [redacted] **months** when stored in the recommended container closure system and under the proposed storage conditions (25°C/60%RH) is granted.

Drug Product – XTANDI Capsules, 40 mg

XTANDI (enzalutamide) Capsules are formulated as opaque white to off-white, liquid-filled soft gelatin capsules. Each capsule contains 40 mg of enzalutamide in a solution of caprylocaproyl polyoxyglycerides, NF [redacted]. The capsules also contain antioxidants (butylated hydroxyanisole, NF and butylated hydroxytoluene, NF). The Applicant provided sufficient documentation to support the suitability of the gelatin capsules. The commercial product will be packaged in a 300-cc 120-count HDPE bottle with a [redacted] closure lined with an induction seal.

The manufacturing process consists of conventional unit operations, including [redacted] finished product packaging. Identified review issues centered around the comparability of the packaging configuration of stability samples relative to that intended for commercialization, the non-acceptability for [redacted] testing from the drug product specification, as well as the corresponding qualification of the commercial HDPE bottles. The Applicant was also asked to harmonized the proposed release and stability specifications. As captured in the Chemistry Review, these deficiencies were resolved during the review clock. Acceptable container/carton labeling was received on 21-AUG-2012.

The Applicant proposed **a 24 month expiry** for this product when stored in the commercial packaging at 20°C to 25°C (68°F to 77°F). Based on the stability data provided and in accordance with ICH Q1E, the Agency grants the proposed expiry. There is no need for additional confirmatory language in the action letter as there is no disagreement between the Applicant's proposed expiration dating period and that granted by the Agency.

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/s/

SARAH P MIKSINSKI
08/29/2012

NDA 203415

Enzalutamide

Medivation Inc.

CMC Team Review:
Gaétan Ladouceur, Ph.D. (Drug Substance)

Office of New Drug Quality Assessment
Division I Branch II
for
The Division of Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 203415

2. REVIEW #: 1

3. REVIEW DATE: 22-Aug-2012

4. REVIEWER: Gaetan Ladouceur, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 74563 submission	01-Mar-2007
CMC Review # 1 (Sue-Ching Lin)	02-May-2007
CMC Review # 2 (Sue-Ching Lin)	28-Jun-2007
EOP 2 (CMC) Meeting Minutes	28-Sep-2009
Type C (CMC) Meeting Minutes	06-Dec-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original NDA Submission	SD 000	22-May-2012
Amendment (SR 008)	SD 008	12-Jul-2012
Amendment (SR 009)	SD 009	13-Jul-2012
Amendment (SR 010)	SD 010	17-Jul-2012
Amendment (SR 011)	SD 011	17-Jul-2012
Amendment (SR 013)	SD 013	23-Jul-2012
Amendment (SR 016)	SD 017	07-Aug-2012

7. NAME & ADDRESS OF APPLICANT (last updated on 18-Jul-2012):

Name: MEDIVATION Inc
Address: 525 Market Street
36th Floor
San Francisco, CA 94105
Representative: Lynn Sealy, Chief Medical Officer
Telephone: 415-829-4106

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Xtandi®
b) Non-Proprietary Name:	Enzalutamide
c) Code Name/# (ONDQA only):	NA
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	1
• Submission Priority:	P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Liquid filled soft gelatin capsule

12. STRENGTH/POTENCY: 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

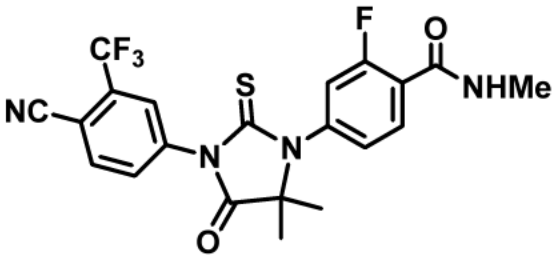
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)	
USAN	enzalutamide
Chemical name	4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide
Alternate Chemical names	4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide 3-(4-Cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one Benzamide, 4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluoro-*N*-methyl
Company names or laboratory code	MDV3100

Empirical Formula	$C_{21}H_{16}N_4O_2S$
Molecular Weight	464.44 g/mol
CAS Registry Number	915087-33-1
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: No DMF were provided in the DS section.

DMF #	TYPE	HOLDER	ITEM REFERENCED/ LOA DATE	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
NA	NA	NA	NA	NA	NA	NA	NA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74563	Original IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	06/20/12	A Inyard
Pharm/Tox	Acceptable	08/03/12	Haw-Jyh (Brian) Chiu
Biopharm	Acceptable	08/15/12	Deepika Arora-Lakhani
LNC	N/A		
Methods Validation	Pending		DPA, St Louis, MO
DMEPA	Proprietary Name Granted	08/03/12	Kimberly A De Fronzo
EA	Categorical exclusion granted.	08/08/12	Debasis Ghosh
Microbiology	Recommend for approval	08/07/12	John Metcalf

DMEPA: Division of Medication Error Prevention and Analysis; DPA: Division of Pharmaceutical Analysis in St. Louis

The Chemistry Review for NDA 203415

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for 'approval'.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Enzalutamide (MDV3100) is a new molecular entity that has (b) (4) and is manufactured (b) (4) It is not hygroscopic and is practically insoluble in aqueous solutions.

The manufacturing process of enzalutamide is a (b) (4) step (b) (4) and the same route was used throughout its entire development. Critical Process Parameters were assessed through Design of Experiments studies for each step of the manufacturing process. Steps (b) (4) were identified has having (b) (4) key Critical Process Parameters. (b) (4)

The drug substance is stable when kept as a solid, but is slightly unstable when submitted to (b) (4). No extraordinary storage precautions are required. A retest period of (b) (4) months at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

(2) Drug Product

The drug product section of this NDA was reviewed by Debasis Ghosh.

B. Description of How the Drug Product is Intended to be Used

Xtandi™ (enzalutamide) is an androgen receptor signaling inhibitor indicated for the treatment of patients with castration-resistant prostrate cancer who have received docetaxel (b) (4).
Four Xtandi™ (enzalutamide) softgel 40 mg capsules should be taken orally once daily with or without food.

C. Basis for Approvability or Not-Approval Recommendation

Approval:
- The applicant provided satisfactory information on the manufacturing, control and stability of the drug substance.
- The applicant provided satisfactory information on the manufacturing, controls and stability of the drug product (see CMC review by Debasis Ghosh).
- All manufacturing sites have received "Overall Acceptable" recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature *{see electronic signature page}*
B. Endorsement Block *{see electronic signature page}*

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/s/

GAETAN LADOUCEUR
08/22/2012

NALLAPERUM CHIDAMBARAM
08/22/2012
I concur

NDA 203415

XTANDI®
(Enzalutamide Capsules)
40 mg

Medivation, Inc

Debasis Ghosh, Ph.D., M. Pharm.,

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

CMC REVIEW OF NDA 203415
For the Division of Drug Oncology Products (DOP1)

Table of Contents

CMC Review Data Sheet

1. NDA 203415

2. REVIEW #: 1

3. REVIEW DATE: 22-Aug-2012

4. REVIEWER: Debasis Ghosh, Ph.D., M. Pharm.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 74563 submission	01-Mar-2007
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CMC Review # 2 (Sue Ching Lin)	28-Jun-2007
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6. SUBMISSION(S) BEING REVIEWED:

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Amendment (SR 008)	SD 008	12-Jul-2012
Amendment (SR 009)	SD 009	13-Jul-2012
Amendment (SR 010)	SD 010	17-Jul-2012
Amendment (SR 011)	SD 011	17-Jul-2012
Amendment (SR 016)	SD 017	07-Aug-2012
Amendment (SR 018)	SD 019	15-Aug-2012
Amendment (SR 019)	SD 020	20-Aug-2012
Amendment (SR 020)	SD 021	21-Aug-2012

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT (last updated on 18-Jul-2012):

Name:	MEDIVATION Inc
Address:	525 Market Street 36th Floor San Francisco, CA 94105
Representative:	Lynn Sealy, Chief Medical Officer
Telephone:	415-829-4106

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Xtandi™
b) Non-Proprietary Name: enzalutamide or MDV3100
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Liquid-filled soft gelatin capsule

12. STRENGTH/POTENCY: 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

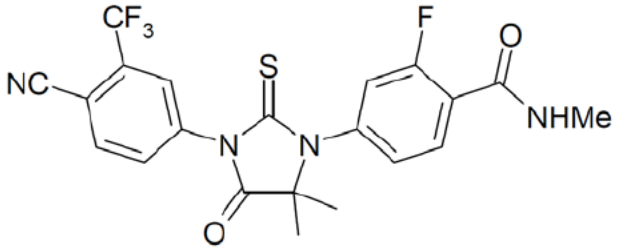
__√___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide

CMC Review Data Sheet

Structural Formula:



Molecular Formula: $C_{21}H_{16}F_4N_4O_2S$
Molecular Weight: 464.44

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	LOA	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	27-Aug-2009	(b) (4)	3,4	Adequate	NA	Reviewed by Zhengfang Ge on 30-Jun-2008 and found to be adequate to support NDA (b) (4) (soft gel capsule).
	IV		13-Mar-2012		1	Adequate	06-Aug-2012	Reviewed by Debasis Ghosh
	IV		25-Jan-2012		4, 7	Adequate	NA	It is a USP/NF monographed compound. The quality information was last reviewed by Susan M Rosencrance on 11/9/2000 and was found to be adequate for the manufacture and control of the excipient. The DMF is active.
	III		07-Nov-2011		7	Adequate	NA	The DMF is active. The (b) (4) was reviewed by Rajiv Agarwal on 6/19/2008 and was found to be adequate. The (b) (4) container closure material was used for oral tablet and capsules and reviewed for the compatibility of solid oral dosage form. Based on MAPP (b) (4), the compatibility of tablet formulation can be extended to the capsule including liquid-filled soft gel capsules. Hence,

CMC Review Data Sheet

DMF #	TYPE	HOLDER	LOA	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)		(b) (4)				DMF is adequate to support NDA 203415.
	III		07-Nov-2011		4, 7	Adequate	NA	The DMF is active. The composition of the (b) (4) is suitable for food contact application in compliance with 21 CFR (b) (4), 21 CFR (b) (4). Based on MAPP (b) (4) (effective 3/22/10), (b) (4) citation for the (b) (4) drug substance is acceptable. In addition, stability data for drug substance established suitability of the (b) (4) for drug substance.. Hence the DMF is adequate to support NDA 203415.
	III		03-Nov-2011		7	Adequate	NA	The DMF is active. Plastic (b) (4) bottle of different configurations have been reviewed by several reviewers and found to be adequate for oral dosage forms. The material compatibility is discussed in DMF (b) (4) below. DMF (b) (4) is adequate for NDA 203415.
	III		07-Nov-2011		7	Adequate	NA	The DMF has been reviewed by Caroline Strasinger on 7/7/10 for the (b) (4) for oral tablets (NDA (b) (4)) and found to be adequate. According to MAPP (b) (4), the compatibility of oral tablet for the material of container closure system can be applicable to oral capsule including liquid filled soft gel capsule. Since the date of the last

CMC Review Data Sheet

DMF #	TYPE	HOLDER	LOA	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)		(b) (4)				DMF review, no additional information on this (b) (4) is provided. The DMF is adequate to support NDA 203415.
	III		04-Nov-2011		7	Adequate	NA	The DMF is active. Last reviewed by Li Shan Hsieh on 7/16/2004 and found to be adequate for film coated tablet . Based on DMF, the (b) (4) is in compliance with 21 CFR (b) (4). Based on MAPP (b) (4) compatibility for tablet and capsules including liquid filled soft gelatin capsule is acceptable. Hence DMF is adequate to support NDA 203415.
	III		16-Nov-2011		7	Adequate	NA	The DMF is active. (b) (4) was reviewed by Yichun Sun on 11/20/2007 and found to be adequate for NDA (b) (4) for oral tablet. Based on the MAPP (b) (4) compatibility as provided in DMF (b) (4) is applicable to tablets, capsule including liquid-filled soft gelatin capsules. Hence the DMF is adequate to support NDA 203415.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74563	Original IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Final decision is deferred to the clinical review team	15-Aug-2012 20-Aug-2012	Stella W Karuri Shenghui Tang
EES	"Overall Acceptable"	20-Jun-2012	A Inyard
Pharm/Tox	recommended for approval	20-Aug-2012	Haw-Jyh (Brian) Chiu and Todd R Palmby
Biopharm	recommended for approval	15-Aug-2012	Deepika Arora-Lakhani
LNC	N/A	N/A	N/A
Methods Validation	Pending	N/A	DPA, St Louis, MO
DMEPA	Proprietary Name Granted	03-Aug-2012	Kimberly A De Fronzo
EA	Categorical exclusion granted (see review)	08-Aug-2012	Debasis Ghosh
Microbiology	'Recommended for approval'	07-Aug-2012	John Metcalf

DMEPA: Division of Medication Error Prevention and Analysis; DPA: Division of Pharmaceutical Analysis in St. Louis

The CMC Review for NDA 203415

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for 'approval' pending satisfactory resolution of the labeling issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

See CMC Review by Dr. Gaetan Ladouceur

(2) Drug Product

Xtandi™, the drug product, is an opaque white to off-white, liquid-filled soft gelatin capsule imprinted in black ink with 'MDV'. Each capsule contains 40 mg of drug substance, enzalutamide, in a solution of caprylocaproyl polyoxyglycerides NF (b) (4) . In addition to (b) (4), the solution contains antioxidants, butylated hydroxyanisole NF (BHA) and butylated hydroxytoluene NF (BHT) (b) (4) of drug substance in the formulation. It has been noted that the drug substance itself is stable in absence of antioxidant. Except the gelatin of capsule shell, all of the inactive ingredients in drug product are free from adventitious agents. The certificate of suitability of gelatin is provided in the submission.

Enzalutamide capsules are intended to be manufactured using conventional unit operations. The development of drug product is based on the QbD principles and risk assessment. The process involve (b) (4) finished product packaging. The details of the manufacturing process is referenced in the Drug Master File (DMF) (b) (4). The applicant provided a copy of the letter of Authorization (LOA) from the DMF holder.

Based on the evaluation, DMF is adequate to support the proposed formulation and is active as of the date of this review. The drug product is manufactured, packaged and tested in various facilities in the United States. The manufacturing and testing sites have received "Overall Acceptable" recommendation from the office of compliance.

The quality attributes of enzalutamide capsules include description, identification, assay, degradants, uniformity of dosage units, antioxidant amounts (BHA and BHT), dissolution, water content, and microbial limits. The proposed specification for each attribute is adequately justified. Validated or compendial analytical method for each attribute is also provided. Please see Biopharm review for the adequacy of the dissolution specification.

Impurity (b) (4) is the (b) (4) process derived degradant found only in the drug product and not detected in the drug substance. Impurity (b) (4) form of enzalutamide, is one of the metabolites of the drug substance and the impurity is considered qualified by virtue of being a metabolite (ICHQ3B). The Pharm-Tox reviewer has confirmed the qualification of the proposed specification. All other related impurities are controlled within the operational parameters.

(b) (4) is used as the excipient in the formulation. Based on the daily dose of 160 mg of enzalutamide, the daily intake of (b) (4) is about (b) (4) The acceptability of the exposure of (b) (4) in this formulation is confirmed by the Pharmacology reviewer.

Xtandi®, enzalutamide soft gel capsule, is intended to be supplied in a 300 cc, (b) (4) opaque high density polyethylene (HDPE) bottles of 120 capsules (30-day supply) with (b) (4) closures lined with induction seals. Based on the evaluation of the container closure system, the container closure provides adequate protection against light and water permeability. Since (b) (4) tends to absorb moisture when exposed to open environment and desiccants can't be used in the container closure system of soft gelatin capsules, it is recommended to store the soft gelatin capsule in a tightly closed container (USP<671>) and kept in a dry place to limit the in-use moisture ingress.

Following the principles of ICHQ1E, a 24 months shelf-life of the drug product can be granted when stored in a tightly closed container at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C.

B. Description of How the Drug Product is Intended to be Used

Xtandi™ (enzalutamide) is an androgen receptor signaling inhibitor indicated for the treatment of patients with castration-resistant prostrate cancer who have received docetaxel (b) (4).

Four Xtandi™ (enzalutamide) softgel 40 mg capsules should be taken orally once daily with or without food.

C. Basis for Approvability or Not-Approval Recommendation

Approval

- The applicant provided satisfactory information on the manufacturing, control and stability of the drug substance. (See CMC-Drug Substance Review by Dr. Gaetan Ladouceur)
- The applicant provided satisfactory information on the manufacturing, controls and stability of the drug product.
- All manufacturing sites have received "Overall Acceptable" recommendation from the Office of Compliance.
- The applicant provided satisfactory information on the container and carton labels.

Pending Issues:

- The applicant should provide the Final Package Insert incorporating all suggested changes.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Debasis Ghosh, Ph.D., M.Pharm., Chemist, Branch II, DNDQA I, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Nallaperumal Chidambaram, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

DEBASIS GHOSH
08/22/2012

NALLAPERUM CHIDAMBARAM
08/22/2012
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Debasis Ghosh, CMC Reviewer
Haripada Sarker, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: debasis.ghosh@fda.hhs.gov
Phone: (301)-796-4093
Fax.: (301)-CMC Reviewer's FAX number

Through: Janice Brown, CMC Lead
Phone: (301)-796-1652
and
Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203415

Name of Product: Enzalutamide (established name) Liquid Filled soft gelatin Capsules, 40 mg

Applicant: Medivation, Inc

Applicant's Contact Person: Lynn Seely, M D, Chief Medical Officer

Address: 201 Spear Street, Third Floor, San Francisco, CA 94105
Telephone: 415-543-3470 Fax: 415-543-3471

Date NDA Received by CDER: **5/22/12**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **na**

Special Handling Required: No

DATE of Request: **June 25, 2012**

DEA Class: N/A

Requested Completion Date: **8/3/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **8/31/2012**

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as descr bed in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 203415

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4.1/4.2
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1/5.2
Supporting Data for Accuracy, Specificity, etc.	3.2.P.5.3 /S.4.3
Applicant's Test Results on NDS and Dosage Forms	
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
HPLC Method 1	Drug Substance Assay and Related Substances	3.2.S.4.2 and 3.2.S.4.3	**0**	Drug Substance assay and impurity evaluation only
HPLC Method 2	(b) (4)	3.2.S.4.2 and 3.2.S.4.3	**0**	Drug Substance impurity (b) (4) (b) (4)
HPLC Method	Drug product identification, Assay, Degradants and Uniformity of dosage Unit	3.2.S.5.2 and 3.2.S.5.3	**0**	Drug Product assay and impurities evaluation only

Additional Comments: None

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a "for cause" reason

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/s/

DEBASIS GHOSH
06/25/2012

JANICE T BROWN
06/26/2012

JEANNIE C DAVID
06/27/2012
ONDQA Methods Validation Project Manager

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 203415/N-000 **Applicant:** Medivation, Inc. **Letter Date:** 21 May 2012

Drug Name: Xtandi **NDA Type:** 505(b)(1) **Stamp Date:** 22 May 2012

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		The NDA is organized in the CTD format and submitted electronically.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?			Not applicable. The drug product is non-sterile.
4	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	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?			Not applicable. The drug product is non-sterile nor preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module 3.2.P.5.1.
7	Has the applicant submitted the results of analytical method verification studies?	X		Module 3.2.P.5.3.; Section 5.3.4.2.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			This reviewer is unaware of any such pre-NDA discussions.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			Not applicable.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: None.

14 June 2012

John W. Metcalfe, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS.

14 June 2012

Stephen E. Langille, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS.

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/s/

JOHN W METCALFE
06/14/2012
The application is fileable from the standpoint of product quality microbiology.

STEPHEN E LANGILLE
06/14/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW FOR NDA 203-415

NDA Number	Original 203-415
Product name, generic name of the active, and dosage form and strength	Xtandi (proposed), enzalutamide (MDV3100), liquid filled soft gelatin capsule, 40 mg
Submission date	21-MAY-2012
Applicant	Medivation, Inc.
Medical Division	Division of Drug Oncology Products
Type of Submission	Quality, NDA 505 (b)(1)
Primary CMC/Quality Reviewer	Debasis Ghosh, Ph.D.
Biopharmaceutics Reviewer	Deepika Arora Lakhani, Ph.D.
CONCLUSION	NDA is FILEABLE.

MDV3100 Drug Product 40 mg is an opaque white to off-white, liquid filled soft gelatin capsule. The proposed indication is for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING: **A.**				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		The following dissolution method is proposed for routine testing: (b) (4)
2.	Is the dissolution test part of the DP specifications?	X		Proposed acceptance criterion: Q = (b) (4) at 30 min
3.	Does the application contain the dissolution method development report?	X		Yes
4.	Is there a validation package for the analytical method and dissolution methodology?	X		The analytical method (HPLC/UV) used for analysis of samples collected during dissolution testing is included in 3.2.P.5.3.
5.	Does the application include a biowaiver request?		X	They have conducted a bioavailability study for BE assessment.
6.	Does the application include an IVIVC model?		X	Not applicable.

7.	Is information on mixing in soft foods and/or drinks provided?			Please see Item#9
8.	Is there any in *vivo* BA or BE information in the submission?	X		This part of the submission will be reviewed by the Office of Clinical Pharmacology.
9.	Proposed dosing information from the draft label			"TRADENAME 160 mg (four 40 mg capsules) administered orally once daily. TRADENAME can be taken with or without food. (2.1)"
B. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
11.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		There are no filing issues. There are no comments to be communicated to the Applicant at this stage.

{See appended electronic signature page}

Deepika Arora Lakhani, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Date

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/s/

DEEPIKA LAKHANI
06/12/2012
NDA is fileable from Biopharmaceutics perspective.

ANGELICA DORANTES
06/13/2012

Initial Quality Assessment
Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

OND Division:	**Division of Oncology Products (DOP 1)**
NDA:	**203-415**
Applicant:	**Medivation, Inc.**
Stamp Date:	**22 May, 2012**
PDUFA Goal Date:	**22 November, 2012 (Priority)**
Established Name:	**Enzalutamide (Code: MDV3100)**
Trade Name	**Xtandi (proposed)**
Chemical Class	**Type-1 (NCE)**
Dosage Form and Strength:	**Capsule – 40 mg**
Route of Administration:	**Oral**
Indication:	**Treatment of patients with castration-resistant prostate cancer who have received docetaxel** (b) (4)
eCTD Reference for CMC	**eCTD.**
Regulatory Filing	**For 505 (b) (1)**
Related IND	**IND 74,563**
Assessed by:	**Haripada Sarker**

	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:		x

Background Summary
NDA 203-415 is submitted for Enzalutamide (MDV3100) capsule, proposed for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4). MDV3100 is a new chemical entity (NCE) formulated as oral capsule. A Type B pre-NDA meeting was held with FDA on 30 March 2012 and a follow-up CMC teleconference meeting on 11 April 2012. In the pre-NDA meeting and CMC teleconference, FDA agreed to receive data not available at the time of this original NDA submission in subsequent submissions. Medivation plans to submit the following NDA amendments containing the requested information to support the Agency's review of the dossier.

- 12-month ICH stability data for MDV3100 Drug Product lot 1152503 will be submitted in June, with stability data for Drug Substance lot 09090060 expected to be submitted in late July.

The Sponsor is requesting a priority review for this NDA. The NDA is submitted as per eCTD format.

Drug Substance (DS)
Enzalutamide (MDV3100) is considered as a novel, small molecule with Biopharmaceutics Classification System (BCS), Class 2. MDV3100 is manufactured as white crystal, practically insoluble in water (b) (4) There is (b) (4)

The structure of MDV3100 is identified as following:

(b) (4)

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

(b) (4)

Comments and Recommendations

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. More than on reviewer is recommended, because of the nature of clinical outcome. If the review is expedited, an EES Exception Request should be filed as soon as possible.

{Haripada Sarker *6-7-2012*

Name of
CMC Lead Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

{Janice Brown} *6-7-2012*

Name of
CMC Lead Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

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/s/

HARIPADA SARKER
06/07/2012

JANICE T BROWN
06/07/2012

Filling Template

NDA Number: 203-415 **Supplement Number and Type:** **Established/Proper Name:** Enzalutamide (Code: MDV3100)

Applicant: Medivation, Inc. **Letter Date:** 21 May, 2012 **Stamp Date:** 22 May, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Yes		Review issue to further verify.

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	Yes		No consult requested.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	Yes		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Yes		
14.	Does the section contain information regarding the characterization of the DS?	Yes		
15.	Does the section contain controls for the DS?	Yes		
16.	Has stability data and analysis been provided for the drug substance?	Yes		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	Yes		Very limited QbD info.
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Yes		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		In drug development section
23.	Have any biowaivers been requested?			Fileable from Biopharm. See biopharm filing review in DARRTS.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?			Review issue. Stat consult requested to analyze stability data.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	Yes		Very limited QbD info.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	Yes		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	Yes		Consult requested.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Yes		LoA provided. See following Table.

Table. DMF References

DMF/IND Number	Holder	Description	LOA Included
[redacted] (b) (4)			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	Yes		DMEPA Consult requested
33.	Have the immediate container and carton labels been provided?	Yes		DMEPA Consult requested

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	Yes		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	Yes		No CMC fileability issue or comment.
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		No	

{Haripada Sarker *6-7-2012*

Name of
CMC Lead
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

Date

{Janice Brown} *6-7-2012*

Name of
CMC Lead
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

Date

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HARIPADA SARKER
06/07/2012

JANICE T BROWN
06/07/2012