

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206162Orig1s000

CHEMISTRY REVIEW(S)

NDA 206162

Lynparza (olaparib) capsules (50 mg)

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

ONDQA Division Director Tertiary Review

Applicant: **Astra Zeneca, Inc.**

Indication: Inhibitor of PARP (Poly (ADPribose) polymerase for treatment of ovarian cancer.

Presentation: Olaparib 50 mg capsules are white, opaque, hard hypromellose capsules. The capsules are marked with "OLAPARIB 50 mg" and the AstraZeneca logo printed in black ink.

Biopharm Recommendation: Acceptable
Establishments Evaluation Report (EER) Recommendation: **Acceptable**

Consults:

EA -	(categorical exclusion per 21CFR25.31 granted)
Statistics -	N/A
Methods Validation -	Acceptable
Clinical Pharm -	Acceptable
Microbiology -	Acceptable
Pharm Toxicology -	Acceptable

Original Submission: February 03, 2014

Re-submissions: N/A

(PMC/PMR):

The applicant agreed to conduct a stability study of commercial product as a Post Marketing Commitment "PMC #2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry."

Drug Substances

Olaparib is a new molecular entity that has no chiral center and is manufactured as a free base. It is not hygroscopic and has a very low solubility in aqueous solutions (classified as Class 4 according to the Biopharmaceutical Classification System). (b) (4)

(b) (4) in olaparib appears to be adequately controlled in the specification of the drug substance. Thus far, there is no evidence of (b) (4) (b) (4) during the proposed shelf life of the drug substance.

The current manufacturing process of olaparib uses (b) (4)

The Critical Process Parameters identified during the development phase led to the implementation of several changes to the (b) (4)

The drug substance is stable in the long-term studies (36 months) and accelerated conditions (6 months). 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.

Conclusion: Drug substance information is satisfactory

Drug product

The olaparib drug product is a 50mg hard capsule manufactured via standard unit operations, including (b) (4) of the olaparib drug substance with the single excipient and capsule fill.

The specifications of the olaparib drug product include testing for appearance, identity by HPLC and UV, assay, (b) (4), degradation products, dissolution, content uniformity and (b) (4). The non-compendial analytical methods were validated. Excluding (b) (4) (which was not measured), satisfactory batch analysis and stability results were provided for the three primary stability batches (lot# 3071641R, 3072918R and 3075510R). No significant trend of change was observed in the reported attributes.

Based on the stability results and analysis of clinical (b) (4) capsule (b) (4), the recommended expiry for the olaparib drug product is eighteen months under long term conditions of 25°C. The applicant agreed, in a Post Marketing Commitment, to conduct repeat ICH primary stability studies for three validation batches. An annual commercial batch will be placed on stability according to the submitted post-approval stability protocol, provided production warrants.

Drug product information is satisfactory**Overall Conclusion:**

There are no pending CMC review deficiencies; therefore, the NDA is recommended for approval.

Ramesh Sood, Ph.D.
Division (I) Director, Acting
ONDQA/CDER/FDA



NDA 206-162

Lynparza (olaparib) capsules (50 mg)

Submitted by Astra Zeneca, Inc.

**CMC Drug Product Review
for the Division of Drug Oncology Products 1 (DOP1)**

**by Anne Marie Russell, Ph.D.
Drug Product Review Chemist
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

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1. NDA 206-162
2. REVIEW #: 1
3. REVIEW DATE: 08-Dec-2014
4. REVIEWER: Drug Substance: Gaetan Ladouceur, Ph.D. (see separate review)
Drug Product: Anne Marie Russell, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original IND 75, 918 submission
CMC end-of-phase-2 meeting
CMC pre-NDA meeting

Document Date

23-Aug-2006
No meeting requested
No meeting requested.

6. SUBMISSION(S) BEING REVIEWED IN THE DRUG PRODUCT CMC REVIEW (see Drug Substance review for other submissions reviewed) :

Submission(s) Reviewed	eCTD Sequence Number	Document Receipt Date	Comments
Original NDA Submission	00	03-Feb-2014	pivotal study #0019
Quality Amendment	12	15-Apr-2014	(unsolicited) Revised analytical method (b) (4) in DP
Quality Amendment	17	25-Apr-2014	Response to Drug Product Information Request #1 (IR) LMG excipient (Q1-5)
Quality Amendment	27	21-May-2014	Partial Response to IR#2 (Q5 Biopharm) bioavailability
Quality Amendment	28	02-Jun-2014	Partial Response to IR#2 (Q2) age of clinical product in pivotal study (Study #0019)
Quality Amendment	29	27-May-2014	Partial Response to IR#2 (Q1, Q3 and Q4 Biopharm) for analytical methods, (b) (4) method and dissolution. Previously submitted via email on 23-May-2014.
Quality Amendment	32	06-Jun-2014	Final response to IR#2/3 Q1 (analytical methods). Information/commitments from 21-May-2014 teleconference.

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Major Clinical Amendment	35	24-Jul-2014	Added clinical studies 0002, 0009, 0012, 0020, 0024 and 0042 (pivotal).
Quality Amendment	35	24-Jul-2014	Response to IR#4 clinical product used in additional clinical studies submitted in major amendment
Quality Amendment	46	16-Oct	Response to IR #5 Capsule Thermal Failure
Quality Amendment	49	04-Nov	Response to IR#6.
Quality Amendment	53	05-Nov	Response to IR#6.
Quality Amendment	51	10-Nov	Response to IR#6
Quality Amendment	55	20-Nov	Response to IR#6
Quality Amendment	By email	24-Nov-2014	Response to IR#6 and late cycle meeting background package
Post Marketing Commitment (Quality)	56	25-Nov	Stability study PMC

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca Pharmaceuticals LP
 Address: 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355
 Representative: Barry Sickels
 Telephone: (302) 886-5895

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Olaparib
- b) Non-Proprietary Name:
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: inhibitor of PARP (Poly (ADPribose) polymerase for treatment of ovarian cancer.

11. DOSAGE FORM: capsule

12. STRENGTH/POTENCY: 50 mg (800 mg daily dose)

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13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

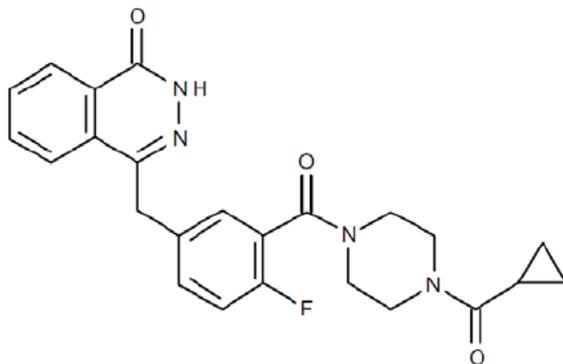
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Figure 1 Chemical structure of olaparib



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4	acceptable	8-Dec-2014	Reviewed by Anne Marie Russell, Ph.D.

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

CMC Review Data Sheet

- 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)

B. Other Documents: None

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Approve	21-Nov-2014	Robert Wittorf
Pharm/Tox	Approve	21-Nov-2014	Tiffany Ricks, Ph.D.
Biopharm	Approve	21-Nov-2014	Okpo Eridiri, Ph.D.
LNC	N/A		
Methods Validation	Acceptable	20-Aug-2014	Jason D. Rodriguez, Ph.D.
DMEPA	Acceptable		
EA	Categorical exclusion	DP review	Anne Marie Russell, Ph.D.
Microbiology	Approve	12-Feb-2014	ERIKA Erika Pfeiler, Ph.D.

EES: Office of Compliance Facility Inspections
 LNC: Labeling and Nomenclature Committee
 DMEPA: Division of Medication Error Prevention and Analysis
 EA: Environmental Analysis

Executive Summary Section

The CMC Review for NDA 206162

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206162 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

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

The applicant agreed to conduct a stability study of commercial product as a Post Marketing Commitment “*PMC #2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including [REDACTED] (b)(4) up to end of expiry.*”

II. Summary of CMC Assessments

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

(1) Drug Product

The olaparib drug product is a 50mg hard capsule manufactured via standard unit operations, including [REDACTED] (b)(4) of the olaparib drug substance with the single excipient and capsule fill.

The specifications of the olaparib drug product include testing for appearance, identity by HPLC and UV, assay, [REDACTED] (b)(4), degradation products, dissolution, content uniformity and [REDACTED] (b)(4). The non-compendial analytical methods were validated. Excluding [REDACTED] (b)(4) (which was not measured), satisfactory batch analysis and stability results were provided for the three primary stability batches (lot# 3071641R, 3072918R and 3075510R). No significant trend of change was observed in the reported attributes.

Based on the stability results and analysis of clinical capsule [REDACTED] (b)(4), the recommended expiry for the olaparib drug product is eighteen months under long term conditions of 25°C. The applicant agreed, in a Post Marketing Commitment, to conduct repeat ICH primary stability studies for three validation batches. An annual commercial batch will be placed on stability according to the submitted post-approval stability protocol, provided production warrants.

Final immediate container and carton labeling was submitted for the proposed commercial packaging configuration and is acceptable.

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Executive Summary Risk Assessment Table for Drug Product

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, stability	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	DP is stable under long term conditions (25°C). Single degradant is controlled to < (b) (4) %.	acceptable	
Physical stability, API	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Medium	(b) (4) API is crystalline (b) (4) has been observed in capsules. (b) (4) measured on release and stability by (b) (4). Controlled to < (b) (4) %.	acceptable	Post Marketing Commitment – stability study which includes characterization (b) (4)
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	(b) (4) Uniformity measured on release.	acceptable	
Microbial limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	Capsule. (b) (4) controlled to < (b) (4) %.	acceptable	
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	Single formulation. Dissolution measured on release and stability.	acceptable	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

Executive Summary Section

(2) Drug Substance – (reproduced from Dr. Gaetan Ladouceur’s Drug Substance Review).

Drug Substance

Olaparib is a new molecular entity that has no chiral center and is manufactured as a free base. It is not hygroscopic and has a very low solubility in aqueous solutions (classified as Class 4 according to the Biopharmaceutical Classification System).

[REDACTED] (b) (4)

[REDACTED] in olaparib appears to be adequately controlled in the specification of the drug substance. Thus far, there is no evidence of [REDACTED] (b) (4) during the proposed shelf life of the drug substance.

The current manufacturing process of olaparib uses [REDACTED] (b) (4)

[REDACTED]

The Critical Process Parameters identified during the development phase led to the implementation of several changes to the [REDACTED] (b) (4)

[REDACTED]

The drug substance is stable in the long-term studies (36 months) and accelerated conditions (6 months). No extraordinary storage precautions are required. A retest period of [REDACTED] (b) (4) months at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

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

Lynparza (olaparib) is a poly (ADP-ribose) polymerase (PARP) inhibitor. It is indicated for patients with deleterious or suspected deleterious germline *BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Eight Lynparza 50 mg capsules (400 mg) are to be taken orally twice daily.

Olaparib capsules are available in 50 mg strength in 112 counts/bottle and 4 bottles/carton packaging configuration. The capsules are recommended to be stored at

Executive Summary Section

20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). An eighteen month expiry at the proposed storage conditions is granted based on the provided stability data. This is to be communicated to the applicant in the action letter.

C. Basis for Approvability or Not-Approval Recommendation:

This new drug application (206162) is recommended to be approved from the CMC perspective. The recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product.

The NDA and all manufacturing sites have received an “Overall Acceptable” recommendation from the Office of Compliance.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

For Drug Product: Anne Marie Russell, Ph.D. Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Haripada Sarker, Ph.D., CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Ali Al Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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

NDA 206162

Olaparib

AstraZeneca Pharmaceuticals

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

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

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1. NDA 206162
2. REVIEW #: 1
3. REVIEW DATE: 21-Nov-2014
4. REVIEWER: Drug Substance: Gaetan Ladouceur, Ph.D.
Drug Product: Anne Marie Russell, Ph.D. (see separate review)
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 75918 submission	08-Aug-2006
CMC Review # 1 (William Timmer)	20-Sep-2006
EOP 2 (CMC) Meeting Minutes	10-Oct-2013
CMC Review # 2 (Gaetan Ladouceur)	09-Jan-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original NDA Submission	SD 000	03-Feb-2014
Amendment (SR 006)	SD 006	24-Mar-2014
Amendment (SR 011)	SD 013	15-Apr-2014
Amendment (SR 029)	SD 028	27-May-2014
Amendment (SR 032)	SD 032	06-Jun-2014
Amendment (SR 039)	SD 040	22-Aug-2014
Amendment (SR 042)	SD 042	05-Sep-2014
Amendment (SR 044)	SD 045	06-Oct-2014

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca Pharmaceuticals LP
Address: 1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355
Representative: Darci L. Bertelsen, Regulatory Affairs Director
Telephone: (302) 886-7355

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lynparza
b) Non-Proprietary Name: Olaparib
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: I
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Anticancer (PARP Inhibitor)

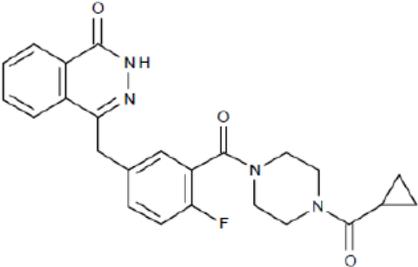
11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 50 mg (800 mg daily dose)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. 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)	
	<p>- International Non-proprietary name (INN): Olaparib</p> <p>- Chemical name (IUPAC): 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one</p> <p>- Company codes: AZD2281; KU-0059436</p>
Empirical Formula	C ₂₄ H ₂₃ FN ₄ O ₃
Molecular Weight	434.46 g/mol
CAS Registry Number	763113-22-0
Structural Formula	 <p>The image shows the chemical structure of Olaparib. It consists of a phthalazine ring system (a benzene ring fused to a six-membered ring containing two nitrogens, one of which is part of a lactam group). This phthalazine core is connected via a methylene group to a para-substituted benzene ring. This benzene ring has a fluorine atom at the 4-position and is further substituted at the 1-position with a piperazine ring. The piperazine ring is connected to a cyclopropylmethyl group via a carbonyl linkage.</p>

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	75918	Original IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES/Panorama	Acceptable for DS	11/30/14	Robert Wittorf
Pharm/Tox	Acceptable	11/21/14	Tiffany Ricks
Biopharm	Acceptable	11/25/14	Okpo Eradiri
Methods Validation	Acceptable	08/20/14	DPA, St Louis, MO
DMEPA	Proprietary Name Granted	07/21/14	DMEPA, Davis Mathew

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

The Chemistry Review for NDA 206162

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206162 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

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

The applicant agreed to conduct a stability study of commercial product as a Post Marketing Commitment “*PMC #2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.*”

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Olaparib is a new molecular entity that has no chiral center and is manufactured as a free base. It is not hygroscopic and has a very low solubility in aqueous solutions (classified as Class 4 according to the Biopharmaceutical Classification System). (b) (4)

(b) (4) in olaparib appears to be adequately controlled in the specification of the drug substance. Thus far, there is no evidence of (b) (4) during the proposed shelf life of the drug substance.

The current manufacturing process of olaparib uses (b) (4)

The Critical Process Parameters identified during the development phase led to the implementation of several changes to the

(b) (4)

The drug substance is stable in the long-term studies (36 months) and accelerated conditions (6 months). 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 (reproduced from Dr. Anne Marie Russell's Drug Product Review)

The olaparib drug product is a 50mg hard capsule manufactured via standard unit operations, including (b) (4) of the olaparib drug substance with the single excipient and capsule fill.

The specifications of the olaparib drug product include testing for appearance, identity by HPLC and UV, assay, (b) (4), degradation products, dissolution, content uniformity and (b) (4). The non-compendial analytical methods were validated. Excluding (b) (4) (which was not measured), satisfactory batch analysis and stability results were provided for the three primary stability batches (lot# 3071641R, 3072918R and 3075510R). No significant trend of change was observed in the reported attributes.

Based on the stability results and analysis of clinical capsule (b) (4), the recommended expiry for the olaparib drug product is eighteen months under long term conditions of 25°C. The applicant agreed, in a Post Marketing Commitment, to conduct repeat ICH primary stability studies for three validation batches. An annual commercial batch will be placed on stability according to the submitted post-approval stability protocol, provided production warrants.

Final immediate container and carton labeling was submitted for the proposed commercial packaging configuration and is acceptable.

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, stability	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	DP is stable under long term conditions (25°C). Single degradant is controlled to < (b) (4) %.	acceptable	
Physical stability, API	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Medium	API is crystalline (b) (4) has been observed in capsules. (b) (4) measured on release and stability by (b) (4). Controlled to < (b) (4) %.	acceptable	Post Marketing Commitment – stability study which includes characterization (b) (4)
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	(b) (4) Uniformity measured on release.	acceptable	
Microbial limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	Capsule. (b) (4) controlled to < (b) (4) %.	acceptable	
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	Single formulation. Dissolution measured on release and stability.	acceptable	

B. Description of how the Drug Product is intended to be used

Lynparza (olaparib) is a poly (ADP-ribose) polymerase (PARP) inhibitor. It is indicated for patients with deleterious or suspected deleterious germline *BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Eight Lynparza 50 mg capsules (400 mg) are to be taken orally twice daily.

Olaparib capsules are available in 50 mg strength in 112 counts/bottle and 4 bottles/carton packaging configuration. The capsules are recommended to be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). An eighteen month expiry at the proposed storage conditions is granted based on the provided stability data. This is to be communicated to the applicant in the action letter.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (206162) is recommended to be approved from the CMC perspective. The recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product.

The NDA and all manufacturing sites have received an "Overall Acceptable" recommendation from the Office of Compliance.

III. Administrative

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

For Drug Substance: Gaetan Ladouceur, Ph.D. Reviewer, ONDQA

B. Endorsement Block *{see electronic signature page}*

Ali Al Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

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IV. Signature Page:

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

METHODS VALIDATION REPORT SUMMARY

TO: Gaetan Ladouceur, CMC Reviewer (for drug substance)
Anne Marie Russell, CMC Reviewer (for drug product)

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: gaetan.ladouceur@fda.hhs.gov
Phone: (301)-796-3878
Fax: (301)-796-9745

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 206162

Name of Product: Olaparib

Applicant: AstraZeneca

Applicant's Contact Person: Lori Chlysta

Address: 1800 Concord Pike, PO Box 8355, Wilmington, DE 19803-8355

Telephone: (302) 886-7355 Fax: (302) 886-2822

Date Methods Validation Consult Request Form Received by DPA: Mar-7-2014

Date Methods Validation Package Received by DPA: Mar-7-2014

Date Samples Received by DPA: Jun-5-2014

Date Analytical Completed by DPA: Aug-20-2014

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached analyst's review and summary of results.



Date: August 20, 2014

From: Jason D. Rodriguez, Ph.D., Chemist, OPS/OTR/ DPA

To: Gaetan Ladoucer, OMPT/CDER/OPS/ONDQA/DNDQAI/BRII
Anne Marie Russell, OMPT/CDER/OPS/ONDQA/DNDQAI/BRII

Through: John Kauffman, Ph.D., Deputy Director, OPS/OTR/ DPA

Subject: Method Validation for NDA206162 Olaparib 50 mg Capsules

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Analytical Procedure for Assay by LC (Drug Substance)
(AstraZeneca., S.4.2A)
2. Analytical Procedure for Organic Impurities by LC (Drug Substance)
(AstraZeneca., S.4.2A)
3. Analytical Procedure for Assay by LC (Drug Product)
(AstraZeneca., P.5..2A)
4. Analytical Procedure for Degradation Products by LC (Drug Product)
(AstraZeneca., P.5..2A)
5. Analytical Procedure for Identification by LC-UV (Drug Product)
(AstraZeneca., P.5..2A)
6. Analytical Procedure for Dissolution (Drug Product)
(AstraZeneca., P.5.1)
7. Identification and (b) (4) (Drug Substance)
8. Quantification of (b) (4) in Olaparib Drug Substance
9. Quantification of (b) (4) in Olaparib capsules (Drug Product)

Link to analyst's work sheets and chromatograms:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880769d87>

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/s/

MICHAEL L TREHY
08/20/2014

JOHN F KAUFFMAN
08/20/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. OMPQ Reviewer: Robert H. Wittorf, PharmD
- 2. NDA/BLA Number: NDA 206162
Submission Date: 03-Feb-2014
21st C. Review Goal Date: TBD
PDUFA Goal Date: 03-Oct-2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	TBD
Established or Non-Proprietary Name (USAN) and strength:	Olaparib (AZD2281), 50 mg
Dosage Form:	Capsule

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY/STANDARD
Applicant Name:	AstraZeneca Pharmaceuticals LP
Responsible Organization (OND Division):	DOP1

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: Ovarian Cancer
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 50 mg (Capsule)
4. Rx/OTC DISPENSED: XRx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation	X			
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	(b) (4)

Process flow chart/diagram of Drug Substance manufacture (taken from eCTD 3.2.S.2.2):

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Figure 1 **Manufacturing route to olaparib**

(b) (4)



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	(b) (4)

Include process flow chart/diagram (taken from eCTD Section 2.3.P.1)

Figure 1 **Flow diagram of olaparib capsule manufacturing process**

(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

Facility related risks evaluated; refer to Drug Product Facility Inspectional History listed below.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

Patheon Pharmaceuticals Inc. (DP manufacturer- FEI# 1510437) was inspected in August 2013 under a PAI inspection. Issues surrounding inadequate investigations, supplier qualification, and control procedures not being established to reduce process variability.

Additional information not covered above

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	PAI Recommendation	Most Recent Milestone	Most Recent EER Compliance Status	Comment
PATHEON PHARMACEUTICALS NC	2/7/2014	1510437	C N	USA	DP Manufacturer DP Release Tester	CHG	08/13-26/2013	PS + GMP 24-Feb-2014	SUBMITTED TO DO	PN	In DO Mailbox for CHG and CTL profile- New Molecular Entity (NME)
ASTRAZENECA PHARMACEUTICALS LP	2/7/2014	2517100	PHI	USA	Packager	CHG	11/28/2011 NAI	Based on Profile 14-Jan-2014	OC RECOMMEND ATION	AC	EES Re-eval: 05-Jul-2015
(b) (4)											
ASTRAZENECA UK LTD	2/7/2014	3002850317	WEU	GBR	Please Obtain From Application	CTL	03/12-16/2012 VAI	PS + GMP 24-Feb-2014	SUBMITTED TO DO	PN	In DO Mailbox for CTL profile NME

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No. The process for both Drug Substance and Drug Product are not complex manufacturing processes atypical to the respective manufacturing facilities.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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/s/

ROBERT H WITTORF
03/14/2014

MAHESH R RAMANADHAM
03/14/2014

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: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: NAME, Methods Validation Requestor, CMC Reviewer: Gaetan Ladouceur (for drug substance) and Anne Marie Russell (for drug product)
NAME, Methods Validation Requestor, CMC Lead: Haripada Sarker
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Gaetan.Ladouceur@fda.hhs.gov, Anne.Russell@fda.hhs.gov, haripada.sarker@fda.hhs.gov
Phone: (301)-301-786-3878 (Gaetan Ladouceur); 301-796-2014 (Anne Marie Russell). 301-796-1747 (Haripada Sarker)
Fax.: (301)- 796-9745

Through: NAME, CMC Lead or Branch Chief (as appropriate): Ali Al Hakim
Phone: (301)- 796-1323
And Youbang Liu
ONDQA Methods Validation Project Manager
Phone: (301)-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 206162

Name of Product: Olaparib (established name)

Applicant: AstraZeneca

Applicant's Contact Person: Lori Chlysta

Address: 1800 Concord Pike, PO Box 8355, Wilmington, DE 19803-8355

Telephone: 302-886-7355 Fax: 302-886-2822

Date NDA Received by CDER: **2/3/2014**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **2/3/2014**

Special Handling Required: No

DATE of Request: **March 5, 2014**

DEA Class: N/A

Requested Completion Date **7/5/2014**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **8/5/2014**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described 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.

MVP Reference #	METHODS VALIDATION REQUEST			NDA #
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Not applicable.				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1 (50 mg capsules)
Specifications/Methods for New Drug Substance(s)				3.2.S.4.
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.7 (DS) and 3.2.P.8 (DP)
Other: Note: DS means drug substance, DP means drug product				
⇒ 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
Not Available (N/A)	Identification and (b) (4)	3.2.S.4.3	0	DS Identity test (b) (4)
N/A	Quantification of (b) (4)	3.2.S.4.3	0	DS (b) (4)
N/A	Assay by LC	3.2.S.4.3	0	DS assay
N/A	Organic Impurity by LC Particle size distribution by laser diffraction	3.2.S.4.3	0	DS impurities DS particle size
N/A	Identification by LC Assay by LC Degradation products by LC (b) (4) Dissolution	3.2.P.5.3	0	Drug Product

Additional Comments: **This NDA is assigned a priority (6 mos) review timeline. The CMC review of this NDA is not dependent on the result of the analytical method validation request.**

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/

GAETAN LADOUCEUR
03/07/2014

ANNE M RUSSELL
03/07/2014

ALI H AL HAKIM
03/07/2014

YOUBANG LIU
03/07/2014



Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206162
2. DATES AND GOALS:

Letter Date: 1/31/2014	Submission Received Date : 2/3/2014
PDUFA Goal Date: 8/3/2014	

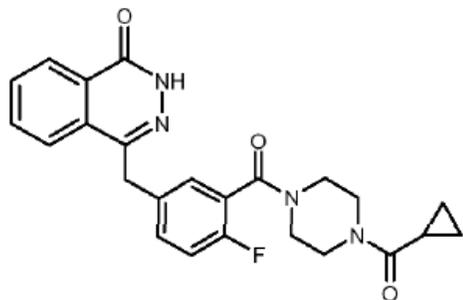
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	N/A
Established or Non-Proprietary Name (USAN):	Olaparib
Dosage Form:	Capsule
Route of Administration	Oral
Strength/Potency	50 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Ovarian cancer.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h): Pharmaceutics International, Inc. (Pii).

7. SUBMISSION PROPERTIES:

Review Priority:	Priority/ Standard Review Requested
Submission Classification (Chemical Classification Code):	Type 1 (New Molecular Entity)
Application Type:	505(b)(1)
Breakthrough Therapy	Yes No
Responsible Organization (Clinical Division):	DOP1, OHOP.

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics			Not applicable
Clinical Pharmacology			Not applicable
Establishment Evaluation Request (EER)	Yes		
Pharmacology/Toxicology			Not applicable
Methods Validation	Yes		
Environmental Assessment	Yes		
CDRH			Not applicable
Other (Micro)	Yes		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications (CMC and Biopharmaceuticals)**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes No
CMC Filing Issues: No
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
CMC Comments for 74-Day Letter: No
1.

Biopharmaceuticals:

Is the Product Quality Section of the application fileable from a Biopharmaceuticals perspective? Yes No
Biopharmaceuticals Filing Issues:
1. None.

Are there potential Biopharmaceuticals review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
Biopharmaceuticals Comments for 74-Day Letter:
1. The dissolution stability data have been reported at only the proposed specification time point of 45 min. Please submit, in excel format, the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes No
Microbiology Filing Issues: no filing issues
See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues. No comment for the 74 day letter.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

CMC Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	Some	No	No

Is a team review recommended?	Yes	No
Suggested expertise for team:	Yes	No
CMC Reviewer:	Gaetan Ladouceur, Ph.D. and Anne Marie Russell, Ph. D.	
Biopharmaceutics Reviewer:	Okpo Eradiri, Ph.D.	
Product Quality Microbiology Reviewer:	Erika Pfeiler, Ph.D.	

Summary of Critical Issues and Complexities
--

See the following individual IQAs

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

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

OND Division: Drug Oncology Products I, OHOP
NDA: 206-162
Applicant: AstraZeneca Pharmaceuticals LP
Regulatory Filing For 505 (b) (1)
Drug Name Olaparib
Related IND/DMF IND 75,918, DMF (b) (4) DMF (b) (4) DMF (b) (4) and
DMF (b) (4)
Assessed by: Haripada Sarker

Note: See data sheet of the filling template for other information.

Background Summary

The application, AstraZeneca introduces the drug product, Olaparib, a PARP (poly ADP ribose polymerase) inhibitor indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapse ovarian cancer. Olaparib is a small new molecular entity, formulated as 50 mg capsule.

Reference is made to Type B Pre-NDA meeting dated October 2, 2013, as well as to pre-NDA CMC specific submission dated October 31, 2013; SD-655, Sequence No. 0577. In CMC and biopharm responses, dated December 3, 2013 (in DARRTS) several CMC issues were communicated to sponsor to consider in the NDA submission. AstraZeneca requested designation of a Breakthrough Therapy for Olaparib under IND 75,918, but the request was not granted.

AstraZeneca considers that the results for the clinical program in gBRCA ovarian cancer to justify the request for priority review under the following category:

Olaparib would provide a safe and effective therapy for the maintenance treatment of adult patients with platinum-sensitive relapse ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation, a disease setting where no therapy currently exists

The CMC information of the NDA is submitted as per eCTDQ format.

Drug Substance (DS)

Olaparib drug substance is an achiral small molecule, manufactured as crystalline (b) (4), and is classified as poorly soluble compound (b) (4),

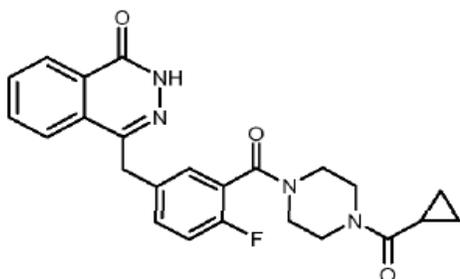
ONDQA Initial Quality Assessment (IQA) and Filing Review For Pre-Marking Applications (CMC and Biopharmaceutics)

(b) (4) potentially relevant in the context of the manufacturing process.

(b) (4)

Olaparib. Manufacturing process also includes the Control of Materials, Control of Critical Steps and Intermediates, in-process-controls and Manufacturing Process Development. A summary of the control strategy is introduced, which provides an overview of the process parameters and analytical controls that indicated to ensure all CQAs for Olaparib along with Critical process parameters (CPP) of above relevant processing steps. The chemical structure of Olaparib is confirmed on batch 060925M1 by using a combination of elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, infra-red (IR) spectroscopy and X-ray diffractometry (XRD). Supporting evidence is provided by the synthetic route and using known starting materials of defined regiospecificity.

The drug substance is identified with following structure.



The proposed drug substance manufacturing site is listed below:

(b) (4)

Olaparib is classified as genotoxic in accordance with the ICH S2 guidance. Therefore, the control of potential genotoxic impurities to the threshold of toxicological concern (TTC) or the staged TTC is not considered. The control of Olaparib DS is included in the following Table 1.

Table 1: Specification for (b) (4) Olaparib Drug Substance Test procedure

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

Test procedure	Acceptance criteria	Method reference
Description	White to pale yellow (b) (4)	Visual inspection
Identification (Chemical) (b) (4)	Conforms with reference spectra	(b) (4)
Olaparib (b) (4)	NMT (b) (4) % w/w	(b) (4)
Assay (b) (4)	(b) (4) % to (b) (4) % w/w	HPLC
Organic impurities ^a		HPLC
(b) (4)	NMT (b) (4) % w/w	
	NMT (b) (4) % w/w	
	NMT % w/w	
Any individual unspecified impurity	NMT % w/w	
Total organic impurities	NMT (b) (4) % w/w	
Particle size		Laser diffraction
(b) (4)	NMT (b) (4) μm	
	NMT μm	
	NMT (b) (4) μm	
Residual solvents ^a		NMR spectroscopy or GC
(b) (4)	NMT (b) (4) % w/w	
	NMT % w/w	(b) (4)
	NMT % w/w	USP/Ph Eur

(b) (4)
NMT Not more than.

Test methods are described along with justification of acceptance criteria. Batch data from 40 batches of (b) (4) Olaparib are presented. These batches are subdivided as follows: Six batches of Olaparib (040502M1, 040611M1, 040611M2, 070112M1, 070116M1 and 070629M1) were manufactured using the synthetic route used during early development. Ten batches of Olaparib (C421 to C436/7) were manufactured using the current synthetic route (b) (4)

The remaining 24 batches were manufactured by the proposed commercial synthetic route and have been considered for the purposes of setting the specification clauses for the drug substance. Summary tables detailing the batches of Olaparib used in the toxicological studies, clinical studies and stability studies performed during the development of Olaparib are presented.

Olaparib DS is stored in (b) (4)

A primary, long-term stability study is ongoing on three batches of Olaparib (C500/1, C500/2 and C500/3) manufactured via the proposed commercial synthetic route and at a scale representative of commercial production. The study is being evaluated over 60 months and is currently at the 36 month time point. All batches are being tested in accordance with ICH Q1A.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

Additionally, stability studies have been set down at stressed conditions (thermal and photolytic stress). Batch C500/1 has been exposed to elevated temperature and elevated light according to ICH Q1B. The storage conditions used and sampling time-points are presented in Table 3 below

Table 3. Storage conditions for the primary stability batches

Condition	Packaging	Batches tested
5°C	(b) (4)	C500/1
25°C/60% RH		C500/1 C500/2 C500/3
30°C/65% RH		C500/1 C500/2 C500/3
40°C/75% RH		C500/1 C500/2 C500/3
50°C/ambient humidity		C500/1
Light ^a		C500/1

^a The light stress was performed using a light source consistent with ICH guidelines providing overall illumination of at least 1.2 million lux hours of visible light and 200 watt hour/m² of UV light.

Based on the available DS stability data, a retest period of (b) (4) months has been proposed when stored (b) (4) at or below 30°C.

Drug Substance Critical Issues

- Verify the designation of regulatory starting material for Olaparib DS.
- Verify CMC issues in pre-NDA meeting (under IND 75918) recommended by Quality reviewer dated October 31, 2013; SD-655.
- Verify the control strategy of the process parameters and analytical controls that ensures CQAs.
- Verify the DS acceptance criteria included in specification.
- Verify the DS stability test data to justify the retest period of (b) (4) months.
- EER information for drug substance needs to be re-examined for accuracy.

Drug Product (DP)

The DP, Olaparib is 50 mg capsules are white opaque hard capsules. The capsules are marked with “OLAPARIB 50 mg” and the AstraZeneca logo printed in black ink. The capsule dimensions are approximately 22 mm in length and 7 mm diameter (size 0). Following Table 4 represents the DP components and composition.

Table 4. Composition of Olaparib 50 mg capsules

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Components	Quantity (mg per unit)	Function	Standard
Olaparib	50	Active ingredient	AstraZeneca
Lauroyl polyoxyl-32 glycerides ^a	(b) (4)	(b) (4)	NF
Hypromellose capsule shell^b			AstraZeneca
Hypromellose	(b) (4)	(b) (4)	USP
Titanium dioxide			USP
Gellan gum			NF
Potassium acetate			USP
Printing ink for capsule shell			
Shellac		(b) (4)	NF
Ferrosoferric oxide			NF
(b) (4)			USP
Isopropyl alcohol			USP
N-butyl alcohol			NF
Propylene glycol			USP
(b) (4)			NF
Total	595		

^a Also known as Lauroyl macrogol-32 glycerides Ph Eur, and referred to throughout the dossier as Lauroyl macrogol-32 glycerides (LMG).

(b) (4)

Based on the outcome of pharmaceutical development, Olaparib capsules have been designed and manufactured as an immediate-release oral formulation, containing 50 mg of Olaparib. Olaparib capsules consist of Olaparib drug substance (b) (4) the (b) (4) lipidic excipient lauroyl macrogol-32 glycerides (abbreviated to 'LMG'), within a hypromellose capsule shell. The capsules are manufactured, using conventional processes that are well established for use in solid oral dosage forms, and packed into bottles.

The proposed DP manufacturing site is listed below:

Patheon Pharmaceuticals Inc
2110 East Galbraith Road
Cincinnati, Ohio 45237-1625
USA

The DP manufacturing process is described with flow diagram along with process controls. Critical process parameters for the manufacture of Olaparib capsules have been identified based on the knowledge gained during drug development. The critical processes parameters are part of the overall control strategy, to ensure the critical quality attributes (CQAs). The overall product quality control strategy are tabulated, and includes a combination of input material specifications, established process parameter ranges, in-process controls and finished product specification and testing.

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The DP specification is presented in following Table 5.

Table 5. Release Specification of Olapararib 50 mg Capsule.

Test procedure	Acceptance criteria	Method reference
Description	White to off white size 0 capsules marked with 'OLAPARIB 50 mg' and the AstraZeneca logo printed in black ink	Description by visual inspection
Identification	Consistent with the retention time and UV spectrum of the reference standard	Identification by LC-UV
Olaparib (b) (4)	NMT (b) (4) % w/w of olaparib (b) (4)	(b) (4)
Assay	(b) (4) % of label claim	Assay by LC
Degradation products (b) (4)	NMT (b) (4) % w/w	Degradation products by LC
Largest individual unspecified degradation product	NMT (b) (4) % w/w	
Total degradation products	NMT (b) (4) % w/w	
Dissolution ^a	Shall comply with the requirements of the United States Pharmacopeia: Q= (b) (4) % at 45 minutes	Dissolution Apparatus 2, LC/UV measurement
Uniformity of dosage units	Shall comply with the requirements of the United States Pharmacopeia	Content uniformity by LC
(b) (4)		

NMT Not more than.

Test methods, and justification of acceptance criteria for each attributes are presented.

Analytical data are presented on 30 batches of Olaparib capsules manufactured at the commercial scale during development. All 30 batches were manufactured at the commercial site, Patheon Pharmaceuticals Inc., Cincinnati, USA. All of the batches indicated to comply with the proposed commercial specification.

The container/closure system of DP includes a (b) (4) mL bottle made of white, high-density polyethylene (HDPE) with a (b) (4) cap made of (b) (4). Inside the cap, are a wax-coated pulp board liner and a seal of aluminum foil lined with (b) (4). The seal is induction-sealed to the bottle for tamper evidence. The bulk capsules are (b) (4). Applicant refers to DMF (b) (4) DMF (b) (4) DMF (b) (4) and DMF (b) (4) for container/closure systems.

DP stability test data are provided on three batches of Olaparib capsules under long-term, accelerated and thermal/light stressed conditions as per following testing protocol (Table 6).

Table 6: Protocol for Primary Studies of Olaparib 50 mg Capsules.

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	5°C	25°C/ 60% RH	30°C/ 65% RH	30°C/ 75% RH	40°C/ 75% RH	40°C/ 75% RH	Photo-stability
Container	Pack	Pack	Pack	Pack	Pack	Open	Pack
Time (month)							
Initial	←----- Y ^(Δ) -----→						
0.5	(R)	(O)	-	-	-	-	Y ¹
1	(R)	(O)	Y	-	Y	Y	-
3	(R)	(O)	Y	Y	Y	-	-
6	(R)	(O)	Y ^(Δ)	Y ^(Δ)	Y ^(Δ)	-	-
9	(R)	(O)	Y	Y	-	-	-
12	(R)	(O)	Y ^(Δ)	Y ^(Δ)	-	-	-
18	(R)	(O)	Y	Y	-	-	-
24 ^a	(R)	(O)	Y ^(Δ)	Y ^(Δ)	-	-	-
36	(R)	(O)	Y ^(Δ)	Y ^(Δ)	-	-	-

- ^a The 24 month timepoint was not tested.
- Y^(Δ) Microbial enumeration testing performed (b) (4)
- (R) Reference only; not normally tested other than for comparison with other conditions.
- (O) Optional testing.
- No sample.
- Y¹ Standard testing, 1 batch only.
- Y Standard testing.

The stability of Olaparib capsules has been assessed by monitoring appropriate chemical and physical characteristics during the stability studies, see Table 7.

Table 7. Analytical Tests used to Assess the Stability of Olaparib Capsules

Test	Specification test	Specification acceptance criteria at end of shelf life
Description ^a	Yes	White to off white size 0 capsules with 'OLAPARIB 50 mg' and the AstraZeneca logo printed in black ink.
Assay	Yes	(b) (4)% of label claim
Degradation products	Yes	(b) (4) NMT (b) (4) % w/w Highest individual unspecified degradation product NMT (b) (4) % w/w Total degradation products NMT (b) (4) % w/w
Dissolution	Yes	Shall comply with the requirements of the European Pharmacopoeia and United States Pharmacopoeia Q = (b) (4) % at 45 minutes
(b) (4)	No	Not applicable
Microbial quality	No	Not applicable

^a The printing ink description specification clause refers to commercial olaparib capsules and not clinical batches of olaparib capsules placed on stability. (b) (4)

One additional batch of capsules was placed on stability within a HDPE bottle. This batch was manufactured at (b) (4) kg scale in the commercial manufacturing facility. The capsules are indicated the same as those for commercial use, without the commercial branding.

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In-use stability studies have been conducted on 2 batches of capsules, which had previously been stored for a period of 36 months at 30°C/75% RH as part of the primary ICH stability studies. Samples of these batches were subsequently stored in open conditions at 25°C/60% RH for 39 days. Post-approval stability protocol and stability commitment for DP has been presented as per ICH primary stability studies.

Based on the primary and supporting stability studies support a shelf-life of (b) (4) months is proposed in the HDPE bottle.

The following product labelling should be used Store at 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

List of Facilities related to CMC of DS and DP are provided. Teicher Agosto (PM, ONDQA) entered the sites in EES.

AstraZeneca requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (a) or (b). To the best of the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

Drug Product Critical Issues

- Verify CMC issues in pre-NDA meeting (under IND 75918) recommended by Quality reviewer dated October 31, 2013; SD-655.
- Verify the control strategy of the process parameters and analytical controls that ensures CQAs.
- Verify the DP acceptance criteria included in specification
- Prepare Method Validation consult for DS as the new molecular entity.
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA.
- Justification of (b) (4)-months expiration based on available stability data
- The DP labeling need to be evaluated for its relevant CMC sections.
- Check EES of DP sites for accuracy.

Comments and Recommendations from Quality (CMC)

The application is fileable; no 74-Day Letter issues regarding drug product stability have been identified at this point. Facilities have been entered into EES for inspection. The manufacturing process is not particularly complex. If priority, two CMC reviewers are recommended for this NDA.

Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

Background: The drug substance, Olaparib, exists in (b) (4)

According to the Applicant, all batches of Olaparib used to manufacture the capsules for clinical trial were (b) (4); the Applicant has not observed (b) (4) in long-term, accelerated or stressed storage conditions. Olaparib exhibits very low solubility (0.11-0.13 mg/mL) in aqueous media across the physiologic pH range; as a result, the drug's solubility is pH-independent. The drug also exhibits poor permeability and is therefore classified as a BCS Class 4 drug. The Applicant obtained a slight improvement in solubility of Olaparib in 1% Polysorbate 80 (0.17 mg/mL), which is then used as the dissolution medium.

Submission: The clinical basis for this NDA is results from a Phase II pivotal study (D0810C00019) and three supporting studies (D0810C00012, D0810C00041, and D0810C00042). Phase III studies are ongoing, and not included in the NDA.

Review: The NDA contains sufficient biopharmaceutics data/information for review. The Biopharmaceutics review will focus on the evaluation and acceptability of the following:

- Adequacy of the dissolution method;
- Adequacy of the proposed dissolution acceptance criterion;

Recommendation: This NDA is fileable from the Biopharmaceutics perspective.

Links:

Biowaiver Request: None

Specifications Table (excludes dissolution): <\\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p5-contr-drug-prod\32p51-spec\specifications.pdf>

Dissolution Method Development: <\\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p2-pharm-dev\pharmaceutical-development-product.pdf>

Dissolution Method Procedure: <\\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p5-contr-drug-prod\32p52-analyt-proc\analyt-dissolution.pdf>

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FILING REVIEW CHECKLIST

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		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	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.			Not applicable.

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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	Yes		Claim of categorical exclusion has been provided.

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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?		No	Some QbD elements are utilized to justify the attributes.
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	

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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		
23.	Have any biowaivers been requested?	Yes		
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?	Yes		Stability data and analysis been provided to support the commercially viable shelf-life.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	Some QbD elements are utilized to justify the attributes.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

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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		

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 below for detail.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	Yes	Not applicable
	III			Yes	Not applicable
	III			Yes	Not applicable
	III			Yes	Not applicable

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

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The following dissolution method is proposed for routine testing: USP 2, 100 rpm, 1000 mL of 1% Polysorbate 80 in water, with sinker.
35.	Is the dissolution test part of the DP specifications?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Q = $\frac{(b)}{(4)}$ % at 45 min.
36.	Does the application contain the dissolution method development report?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 3.2.P.2 under Pharmaceutical Development.
37.	Is there a validation package for the analytical method and dissolution methodology?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Elements of method validation are included in section 3.2.P.5.3.
38.	Does the application include a biowaiver request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	One 50 mg strength is submitted for approval.
39.	Does the application include data supporting the biowaiver?	<input type="checkbox"/>	<input type="checkbox"/>	N/A
40.	Does the application include an IVIVC model?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Is information such as BCS classification mentioned, and supportive data provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The solubility and permeability data are summarized in Tables 2 and 3 in the package; based on that data, the Applicant concluded that olaparib is a BCS Class 4 compound.
42.	Is information on mixing the product with foods or liquids included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The dosage form comprises encapsulated drug $\frac{(b)}{(4)}$ $\frac{(b)}{(4)}$, lipidic $\frac{(w)}{(w)}$ lauroyl macrogol-32 glycerides, LMG. $\frac{(b)}{(4)}$
43.	Is there any <i>in vivo</i> BA or BE information in the submission?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This will be a 505(b)(1) NDA. OCP will review all BA/BE/PK data.

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FILING CONCLUSION				
	Parameter	Yes	No	Comment
44.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>		
45.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
46.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
47.	Are there any potential review issues identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The dissolution stability data have been reported at only the proposed specification time point of 45 min. Please submit, in excel format, the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications (*CMC and Biopharmaceutics*)**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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