CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206947Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 206947

From: Gaetan Ladouceur, Ph.D and Amit K. Mitra Ph.D.

Through: Ali Al-Hakim, Ph.D

Date: 2/5/2015

Re: NDA 206947- Memo to File

Refer to the Drug Substance and Drug Product Primary Quality Assessment reviews of NDA 206947, dated 01/15/2015, in which this NDA was recommended for 'approval' pending acceptable overall recommendation from the Office of Compliance.

On 02/05/2015, the Office of Compliance made an "acceptable" overall manufacturing inspection recommendation facilities inspection recommendation (see Panorama entry by Robert Wittorf, PharmD). Therefore, from the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is now recommended for 'approval'.

Gaetan Ladouceur -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000762538, cn=Gaetan Ladouceur -A
Date: 2015.02.05 16:33:02 -05'00'

Amit K. Mitra -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amit K. Mitra -S, 0.9.2342.19200300.100.1.1=1300102436
Date: 2015.02.05 16:35:17 -05'00'

Ali H. Al-Hakim -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093815, cn=Ali H. Al- Hakim -A
Date: 2015.02.05 16:38:35 -05'00'

NDA 206-947

LENVIMA (lenvatinib) capsules
4 and 10 mg
Eisai, Inc.
Drug Product Review

Amit K. Mitra, Ph.D
Branch II/ONDP

for
Division of Drug Oncology Products (Div 2)

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-947

2. REVIEW #:1

3. REVIEW DATE: 30-OCT-2014

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	14-AUG-2014
Amendment	26-DEC-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Eisai, Inc.
Address:	155 Tice Boulevard, Woodcliff Lake, NJ 07677
Representative:	Susan Mayer
Telephone:	(201)-949-4831

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lenvima
b) Non-Proprietary Name (USAN): Lenvatinib
c) Code Name/# (ONDC only): E7080, ER-203492-13
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Treatment of patients with progressive readioiodine-refractory differentiated thyroid cancer

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 4 and 10 mg

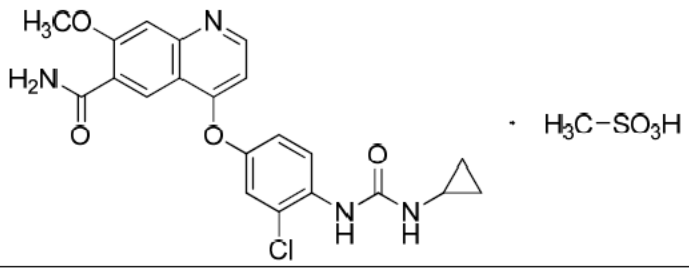
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x____Not a SPOTS product

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

Chemical Name(s)	
- International Non-proprietary name (INN): Lenvatinib **Nationally Approved Names (USAN):** Lenvatinib mesylate - Chemical name (IUPAC): 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate - Company codes: E7080, ER-203492-13	
Empirical Formula	$C_{21}H_{19}ClN_4O_4 \bullet CH_4O_3S$
Molecular Weight	522.96 g/mol (mesylate), 426.86 (free base)
CAS Registry Number	857890-39-2
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)		1	Adequate	Dr. A, K. Mitra, 12-JAN-2015	Adequate
	III			7	Adequate	Dr. R. Agarwal, 24-MAR-2010/ Dr. P. J. Baucom, 26-SEP-2014	No substantial change from those submissions
	III			7	Adequate (Annual Report-16)	Dr. D. Klein, 25-DEC-2012	Adequate to support NDA (b) (4) (b) (4). No substantial change since then.

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4) 113656, (b) (4)	Supporting documents

18. STATUS:

ONDQA

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		Robert Wittorf
Pharm/Tox	Acceptable	17-JAN-2015	Emily Fox
Biopharm	Satisfactory	13-JAN-2015	Dr. O. Eradin
LNC	N/A		
Methods Validation	Pending*		DPA, St. Louis, MO
DMEPA	Proprietary name Satisfactory	23-DEC-2014	Mr. T. D. Bridges
EA	Satisfactory	14-JAN-2015	Dr. A. K. Mitra
Microbiology	Satisfactory	Panorama	Dr. J. Cole

* Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 206-947

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is approvable from CMC perspective pending acceptable cGMP recommendation from Office of Compliance.

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

The following phase 4 commitment was sought via a teleconference with the applicant on 08-JAN-2015:

1) Adopt a limit test for level (b) (4) in the drug product and include a specification.
2) Submit the analytical method and its validation.
3) Provide data in support of limits of the specification.

The information may be submitted in a prior approval supplement with a request to sunset the test and acceptance criterion based on the submitted data.

In an amendment, dated 13-JAN-2015 the applicant made the following PMC.

Proposed Post-Marketing Commitment:

Commit to submitting a prior approval supplement with a request to sunset the test and acceptance criterion based on the submitted data with the following information:

1. A limit test for level (b) (4) of the drug substance in the drug product including the analytical method and its validation.
2. Supporting data for the limits.
3. Dates and milestones for completion of the above tasks.

Eisai formally commits to the above PMC by 30 June 2015.

II. Summary of Chemistry Assessments

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

Drug Substance

Lenvatinib is a new molecular entity that has no chiral center and is manufactured as a mesylate salt. It is not hygroscopic and has a very low solubility in aqueous solutions. (b) (4)

(b) (4)

Based on a QbD approach, a new manufacturing process was implemented during development (b) (4)

(b) (4)

The drug substance is stable in the long-term studies (24 months) and accelerated conditions (6 months). A retest period of (b) (4) months at the recommended (b) (4) storage conditions is supported by drug substance stability data.

Drug Product

Lenvatinib is an oral multiple receptor tyrosine kinase (RTK) inhibitor. It is indicated for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC). The recommended starting dose of lenvatinib is 24 mg taken once daily (QD).

The proposed lenvatinib drug product is an immediate release hypromellose capsules at two different strengths. The 4 and 10 mg (b) (4) . The 4 mg capsule is a yellowish red body and a yellowish red cap, marked in black ink with "∈" on the cap and "LENV 4 mg" on the body. The 10 mg capsule is a yellow body and a yellowish red cap, marked in black in with "∈" on the cap and "LENV 10 mg" on the body. The inactive components of (b) (4) are calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropyl cellulose, (b) (4) hydroxypropyl cellulose, talc and hypromellose capsules. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol. All excipients are of compendial grade except for the hypromellose capsules. The CMC information of the hypromellose capsules are referred to DMF (b) (4) and the DMF is adequate to support the NDA. An Information Request was sent to the applicant on the functional attributes of the excipients and their impact of drug product quality. The applicant's response is satisfactory according to the current regulatory standard. The manufacturing process for the drug product involves (b) (4) . LENVIMA (lenvatinib)

capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card for 10, 14, 20 or 24 mg daily-dose. Lenvatinib has been formulated in two orally administered dosage forms (film coated tablets and capsules) different phases of clinical development. The tablets used in early clinical trials were manufactured (b) (4) [redacted] For details of the discussion see the review of section P.5.1. The reviewer also used a FMECA (Failure mode, effects and critically analysis and risk priority number (RPN) to convey the risk associated with the potential of critical quality attributes, post approval (see Section P.5.1 for details of the risk assessment and the risk assessment table below).

The applicant is proposing a shelf life of 36 months for the drug product and it is granted. "Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)".

Several Information Requests were sent to the applicant. One of the Information requests deals with the (b) (4) [redacted] data without analytical method and its validation. Even though the analytical method is not available pre-approval an alternate but less reliable control strategy (dissolution) is available for quality control. Therefore, a post-approval commitment is recorded with the approval recommendation (see Section B of the Recommendation).

Drug Product Risk Assessment Table

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	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	The applicant's approach for risk mitigation is satisfactory. The related substances are being monitored.	Based on 24 months satisfactory long term stability data a 36 months shelf life is granted (see stability section of	The stability data should be monitored, post approval
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Not satisfactory (post approval commitment is being sought)	Potential variation in clinical response from batch to batch. Analytical method not provided.	Post-approval supplement evaluation
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	Content uniformity is tested for every batch. Weight variation is the	(b) (4) The process is with medium risk	Evaluate batch results during review and inspection
Dissolution	• Formulation Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Discriminatory nature of the dissolution method is being evaluated by the Biopharm	High risk (at this point of review)	See comments of the Dissolution reviewer

Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Every batch is tested for microbial attributes	Satisfactory to the microbiology reviewer	Evaluate batch results during review and inspection inspection

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

The drug product is proposed to be marketed in 10, 14, 20 and 24 mg daily dose cartons with combination of 4 and 10 mg capsules. The recommended daily dose of Lenvima is 24 mg taken once daily. The daily dose is to be modified according to the dose/toxicity management plan provided in the Dosage and Administration section of the PI.

The applicant has provided sufficient stability data for a 36 months tentative shelf life under long term storage conditions.

The applicant is proposing a shelf life of 36 months for the drug product and it is granted.The storage condition is: "Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)".

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate information for approval. The residual risk in product quality is being addressed by post-approval commitment Section B of the Recommendations section.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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Amit K. Mitra -S

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Date: 2015.01.13 16:56:48 -05'00'

Ali H. Al-Hakim -S

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Date: 2015.01.13 17:00:39 -05'00'

NDA 206947

Lenvatinib

Eisai Pharmaceuticals

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 206947

2. REVIEW #: 1

3. REVIEW DATE: 14-Jan-2015

4. REVIEWER: Gaetan Ladouceur, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND (b) (4) submission	31-Mar-2005
CMC Review # 1 (Ruth Wager)	25-Apr-2005
CMC Review # 2 (Amit Mitra)	20-Apr-2012
CMC Review # 3 (Haripada Sarker)	26-Jun-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original NDA Submission	SD 001	08-Aug-2014
Amendment (SR 016)	SD 017	26-Nov-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Eisai Inc.
Address:	155 Tice Boulevard Woodcliff Lake, NJ 07677
Representative:	Susan Mayer, Global Regulatory Affairs Director
Telephone:	(201) 949-4831

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Lenvima
b) Non-Proprietary Name:	Lenvatinib
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: Radioiodine-refractory differentiated thyroid cancer

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 4 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

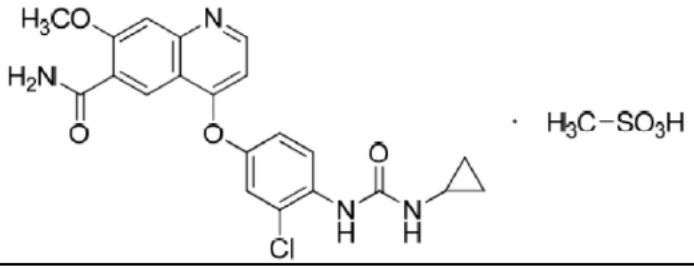
14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

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)	
- International Non-proprietary name (INN): Lenvatinib **Nationally Approved Names (USAN):** Lenvatinib mesylate - Chemical name (IUPAC): 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate - Company codes: E7080, ER-203492-13	
Empirical Formula	$C_{21}H_{19}ClN_4O_4 \bullet CH_4O_3S$
Molecular Weight	522.96 g/mol (mesylate), 426.86 (free base)
CAS Registry Number	857890-39-2
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	(b) (4)	Original IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	--	Robert Wittorf
Pharm/Tox	Acceptable	01/14/15	Emily Fox
Biopharm	Acceptable	01/14/15	Okpo Eradiri
Drug product	Acceptable	01/14/15	Amit Mitra
Methods Validation	Pending*	--	DPA, St Louis, MO
DMEPA	Proprietary Name (Acceptable)	12/23/2014	DMEPA, Sue Kang

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

* Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The Chemistry Review for NDA 206162

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is approvable from CMC perspective pending adequate recommendation from Office of Compliance.

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

The following phase 4 commitment was sought via a teleconference with the applicant on 08-JAN-2015:
1) Adopt a limit test for level (b) (4) in the drug product and include a specification.
2) Submit the analytical method and its validation.
3) Provide data in support of limits of the specification.
The information may be submitted in a prior approval supplement with a request to sunset the test and acceptance criterion based on the submitted data.
The specific tasks with dates and milestones are recommended to be attached to the Action letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Lenvatinib is a new molecular entity that has no chiral center and is manufactured as a mesylate salt. It is not hygroscopic and has a very low solubility in aqueous solutions. (b) (4)

Based on a QbD approach, a new manufacturing process was implemented during development (b) (4)

The drug substance is stable in the long-term studies (24 months) and accelerated conditions (6 months). A retest period of (b) (4) months has been granted at the recommended (b) (4) storage conditions (b) (4) which is supported by drug substance stability data.

(2) Drug Product (reproduced from Dr. Amit Mitra's Drug Product Review)

Lenvatinib is an oral multiple receptor tyrosine kinase (RTK) inhibitor. It is indicated for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC). The recommended starting dose of lenvatinib is 24 mg taken once daily (QD).

The proposed lenvatinib drug product is an immediate release hypromellose capsules at two different strengths. The 4 and 10 mg (b) (4). The 4 mg capsule is a yellowish red body and a yellowish red cap, marked in black ink with "∈" on the cap and "LENV 4 mg" on the body. The 10 mg capsule is a yellow body and a yellowish red cap, marked in black in with "∈" on the cap and "LENV 10 mg" on the body. The inactive components of (b) (4) are calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropyl cellulose, (b) (4) hydroxypropyl cellulose, talc and hypromellose capsules. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol. All excipients are of compendial grade except for the hypromellose capsules. The CMC information of the hypromellose capsules are referred to DMF (b) (4) and the DMF is adequate to support the NDA. An Information Request was sent to the applicant on the functional attributes of the excipients and their impact of drug product quality. The applicant's response is satisfactory according to the current regulatory standard. The manufacturing process for the drug product involves (b) (4) . LENVIMA (lenvatinib) capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card for 10, 14, 20 or 24 mg daily-dose. Lenvatinib has been formulated in two orally administered dosage forms (film coated tablets and capsules) different phases of clinical development. The tablets used in early clinical trials were manufactured (b) (4) The reviewer also used a FMECA (Failure mode, effects and criticality analysis and risk priority number (RPN) to convey the risk associated with the potential of critical quality attributes, post approval (see Section P.5.1 for details of the risk assessment and the risk assessment table below).

Several Information Requests were sent to the applicant. One of the Information requests deals with the (b) (4) data without analytical method and its validation. Even though the analytical method is not available pre-approval an alternate but less reliable control strategy (dissolution) is available for quality control. Therefore, a post-approval commitment is recorded with the approval recommendation (see Section B of the Recommendation).

Drug Product Risk Assessment Table

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	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	The applicant's approach for risk mitigation is satisfactory. The related substances are being monitored.	Based on 24 months satisfactory long term stability data a 36 months shelf life is granted (see stability section of the review)	The stability data should be monitored, post approval
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Not satisfactory (post approval commitment is being sought)	Potential variation in clinical response from batch to batch. Analytical method not provided.	Post-approval supplement evaluation
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	Content uniformity is tested for every batch. Weight variation is the process control	(b) (4) The process is with medium risk	Evaluate batch results during review and inspection
Dissolution	• Formulation Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Discriminatory nature of the dissolution method is being evaluated by the Biopharm reviewer	High risk (at this point of review)	See comments of the Dissolution reviewer
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Every batch is tested for microbial attributes	Satisfactory to the microbiology reviewer	Evaluate batch results during review and inspection

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

The drug product is proposed to be marketed in 10, 14, 20 and 24 mg daily dose cartons with combination of 4 and 10 mg capsules. The recommended daily dose of Lenvima is 24 mg taken once daily. The daily dose is to be modified according to the dose/toxicity management plan provided in the Dosage and Administration section of the PI.

The applicant has provided sufficient stability data for a 36 months tentative shelf life under long term storage conditions.

The storage condition is: "Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)". The applicant is proposing a shelf life of 36 months for the drug product and it can be granted.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate information for approval. The residual risk in product quality is being addressed by post-approval commitment Section B of the Recommendations section.

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

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

III. Signature Page:

Digitally signed by Gaetan Ladouceur -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000762538, cn=Gaetan Ladouceur -A
Date: 2015.01.13 14:11:15 -05'00'

Ali H. Al-Hakim -S

Digitally signed by Ali H. Al-Hakim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093815, cn=Ali H. Al- Hakim -S
Date: 2015.01.13 14:52:16 -05'00'

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

I. Review Cover Sheet

1. OMPQ Reviewer: Robert H. Wittorf, PharmD.

2. NDA/BLA Number: NDA 206947
   Submission Date: 14-Aug-2014
   21st C. Review Goal Date: 15-Feb-2015
   PDUFA Goal Date: 13-Apr-2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	TBD
Established or Non-Proprietary Name (USAN) and strength:	Lenvatinib
Dosage Form:	CHG

4. SUBMISSION PROPERTIES:

Review Priority :	Priority
Applicant Name:	Eisai Inc.
Responsible Organization (OND Division):	DOP2

II. Application Detail

1. INDICATION: For the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer

2. ROUTE OF ADMINISTRATION: Oral (Capsule)

3. STRENGTH/POTENCY: Two strengths: 4 mg and 10 mg

4. Rx/OTC DISPENSED: X☐Rx ☐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			Priority Designation- Six Month Review

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		Location of facilities provided as attachment to 356h.
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) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X		
			X	
			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.

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	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

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

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

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

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 If yes, please identify the sites in the above chart. Initial review of the application supports a KTM for the manufacturing of the drug product. (b) (4) Initial review of the DS section could potentially warrant a KTM (b) (4)
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)

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

/s/

ROBERT H WITTORF
10/08/2014

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

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206947
2. DATES AND GOALS:

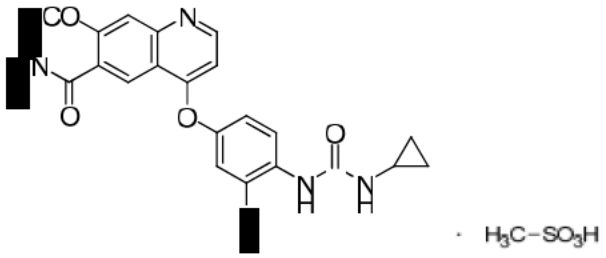
Letter Date: 8/14/2014	Submission Received Date : 8/14/2014
PDUFA Goal Date: 2/14/2015 (P or S which is not finally determined)	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	LENVIMA/TBD
~~Established or~~ Non-Proprietary Name (USAN):	lenvatinib
Dosage Form:	Capsule
Route of Administration	Oral
Strength/Potency	4 mg, 10 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: the treatment of patients with progressive radioiodine-refractory differentiated thyroid cancer (RR-DTC).

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h): Eisai

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	No
Responsible Organization (Clinical Division):	DODP2, OHOP.

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	Not applicable
Clinical Pharmacology		X	Not applicable
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	Determined by the primary reviewer
Methods Validation	X		
Environmental Assessment		X	Determined by the primary reviewer. Claim of categorical exclusion has been provided.
CDRH		X	Not applicable
Other (Micro)	X		

Overall Filing Conclusions and Recommendations

CMC:

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

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

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues:
1. None.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes
Biopharmaceutics Comments for 74-Day Letter:
1. The dissolution stability data have been reported at only the proposed specification-sampling time point of (b) (4) min. Please submit, in SAS transport file format, the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations. If multiple time point profiling data were not collected, perform a full profiling (n=12) of the registration and clinical batches at the current stability time point using the following sampling times: 10, 15, 20, and 30 minutes and submit these data to the NDA. Thereafter, continue with the full dissolution profiling for the remainder of the stability program. 2. The experimental data in support of your proposed dissolution method's suitability for your product is missing from the NDA. Submit the dissolution method development report supporting the selection of the proposed dissolution test. Include in the report, the developmental parameters (i.e., rationale for selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, surfactant type and amount, assay, sink conditions, etc.) that support the proposed dissolution method as optimal for your product. Your proposed dissolution acceptance criterion should be based on the complete dissolution profile data (n=12) for all pivotal clinical and primary stability/registration batches. For your immediate release product, the selection of the specification time point should be where Q=(b) (4)% dissolution occurs.

Microbiology:

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

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		
CMC Reviewer: Amit Mitra, Ph.D. and Gaetan Ladouceur, Ph. D.		
Biopharmaceutics Reviewer: Okpo Eradiri, Ph.D.		
Biopharmaceutics Team Leader: Angelica Dorantes, Ph.D.		
Product Quality Microbiology Reviewer: Jessica Cole, Ph.D.		
CMC Lead: Liang Zhou, Ph.D.		
Chief, CMC Branch II: Ali Al Hakim, Ph.D.		

Summary of Critical Issues and Complexities

See the following individual IQAs

Following are the Drug Substance (DS) and Drug Product (DP) information as per IQP 5106 (Attachment-1)

Initial Quality Assessment

Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
NDA 206947

Background Summary

Lenvatinib is claimed to be an oral multiple receptor tyrosine kinase (RTK) inhibitor and selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, in addition to other proangiogenic and oncogenic pathway related RTKs, including fibroblast growth factor (FGF) receptors, FGFR1, 2, 3, and 4; the platelet-derived growth factor (PDGF) receptor, PDGFRα; KIT; and RET.

The proposed indication for lenvatinib is the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC).

Lenvatinib is a small new molecular entity, formulated as 4 mg and 10 mg capsules. The recommended starting dosage of lenvatinib is 24 mg taken once daily (QD).

Drug Substance and Drug Product

1. Document the drug type (e.g., API, dosage form, delivery system).

It is a small new molecular entity, formulated as 4mg and 10 mg capsules, administered orally.

2. Identify the chemical classification code (as required for PDUFA V).

DS Chemical Class: (b) (4)

The chemical structure is confirmed (b) (4) found to be acceptable by the FDA as per the agency's Advice Letter dated 18 May 2012. It is manufactured under cGMP by Eisai Co. Ltd. at its Kashima Plant in Japan.

3. If an innovative technology is proposed in the submission, document it and discuss the consequences for the review process.

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 Palbociclib along with Critical process parameters (CPP) of above relevant processing steps.

3.2 DP is formulated, manufactured and controlled (b) (4)

It is formulated as an immediate release capsule for oral administration at4 mg and 10 mg strengths. The components and compositions of 4 mg and 10 mg capsules are provided.

The DP manufacturing process is described with flow diagram along with process controls. Critical process parameters for the manufacture of Palbociclib 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.

4. Identify what consults will be needed to conduct the review.
For consult, See Item 8 under IQA and Filing Review Cover Sheet

5. Identify required facility input for the EES.
Facilities for DS and DP are entered in EES by PM and verified CMC Lead for Inspection by OC.

6. Summarize key issues from the IND phase.
It was transferred from DODP1 to DODP2 (refer to advice Letter in #2)

7. Determine whether there is information (e.g., in the pharmaceutical development, batch analysis and stability sections) for the CMC and Biopharmaceutics reviewers to establish a bridge between the clinical batches and the commercial manufacturing process. The Biopharmaceutics reviewer will determine whether there is information (e.g., dissolution method development report) in an NDA submission.

See Biopharmaceutics IQA for this issue.

8. Determine whether stability data are sufficient to support an expiration date.
12-months DS stability data appears to be acceptable pending acceptable CMC review recommendation.
24-months DP stability data appears to be acceptable pending acceptable CMC review recommendation.

9. List the important DMFs (e.g. drug substance, novel excipients) that are referenced.
For DMF, See section H. MASTER FILES (DMF/MAF) under Review Filling Checklist

9a. Are there letters of authorization?
Yes. See #9 above

9b. Has a deficiency in the DMF been previously identified (e.g., by OGD) and if so has an amendment been submitted?

Not noted. Primary Reviewer may verify and address if any.

9c. Have amendments been submitted since the last review?

Not noted. Primary Reviewer may verify and address if any.

10. Determine whether the application includes Quality by Design elements.
Eisai is not proposing a design space in this submission. Instead, proven acceptable ranges have been identified for operating parameters. Attributes and parameters have been categorized as either critical or non-critical, based on their impact to the product quality. Where a quality attribute has been designated as critical (critical quality attribute or CQA), associated elements of the control strategy will be explained in detail.

The NDA is not formally submitted as QbD application; however, some elements of QbD are applied in DS and DP manufacturing and quality controls. Primary Reviewer might verify the QbD elements as appropriate.

11. Determine whether the Applicant is proposing a comparability protocol.
N/A
Additionally, see Biopharm IQA for this issue.

12. Describe issues with drug name, if any.
Pending Consult for the proposed proprietary name LENVIMA

13. Describe changes between the clinical DP and the proposed commercial DP, if any.

Not noted. Primary Reviewer may verify and address if any.

14. Provide drug substance overview and issues, if any.

Drug Substance Critical Issues

- Verify the designation of regulatory starting material for DS.
- Verify CMC issues in CMC related issues in pre-NDA meeting stage.
- Verify the control strategy of the process parameters and analytical controls that ensures CQAs.
- Verify the DS acceptance criteria included in specification.
- Omission of test for solvents from DS specifications.
- 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.

15. Provide drug substance specification.

The DS controls include detailed explanation of the origin, fate, purge and control of these

impurities, including genotoxic impurities.

16. Provide Drug Product overview and issues (including as appropriate, containers closure issues like leachables), if any.

The registration stability studies for DP capsules will justify the acceptability of the proposed commercial container/closure systems, special in blister packages.

Drug Product Critical Issues

- Verify CMC issues in pre-NDA meeting.
- 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 since it is the new molecular entity.
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA.
- Justification of proposed 36-months expiration based on supportive 24-months stability data
- The DP labeling need to be evaluated for its relevant CMC sections.
- Check EES of DP sites for accuracy.

17. Provide composition of drug product.
See above summary

The DP manufacturing process is described with flow diagram along with process controls. Critical process parameters for the manufacture of Palbociclib 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.

18. Provide drug product specification.

The DP specification is provided.

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

Applicant provided summaries of data including Microbial method and acceptance criterions have been established for DP capsules.

Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

(b) (4)

Submission: Ten safety and efficacy studies, including one pivotal Phase 3 study in 392 patients, were conducted in support of the clinical basis for approval of this NDA. Sixteen clinical pharmacology studies were also conducted.

The dissolution information/data are included in the links below.

- *Specifications Table (excludes dissolution):* \\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p51-spec\specifications.pdf
- *Dissolution Method Validation:* *\\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p53-val-analyt-proc\dissolution.pdf*
- Dissolution Method Procedure: \\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p52-analyt-proc\dissolution.pdf

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;
- Adequacy of data supporting bridging throughout product development

Recommendation*:* NDA 206947 is fileable from the Biopharmaceutics perspective. However, the Applicant is being requested to provide additional information/data. Refer to the Biopharmaceutics information request comments to be sent to the Applicant in the 74-Day letter in page 3 of this document.

Overall CMC Recommendation: This NDA is fileable.

Comments and Recommendations from Quality (CMC)
The application is fileable; no 74-Day Letter issues have been identified at this point. Facilities have been entered into EES for inspection. However, Biopharmaceutics comments for the 74-Day Letter are listed on page 3.

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

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 *potential* filing issue or a *potential* 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.

	Parameter	Yes	No	Comment
7.	Are the drug substance manufacturing sites identified in FDA's 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 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		

	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: • 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.

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	
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	
F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	Yes		Consult request will be made to Division of Pharmaceutical Analysis Attn: Michael Trehy, PhD Suite 1002 1114 Market Street St. Louis, MO 63101
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		

Table. DMF Information.

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

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?	X		The following dissolution method is proposed for routine release and stability testing: USP 2, 50 rpm, 900 mL of 0.1M HCl.
35.	Is the dissolution test part of the DP specifications?	X		Q = (b) (4) % at (b) (4) min.
36.	Does the application contain the dissolution method development report?		X	See request for dissolution method development report above.
37.	Is there a validation package for the analytical method and dissolution methodology?	X		Section 3.2.P.5.3.5.
38.	Does the application include a biowaiver request?		X	Both the 4 and 10 mg strengths were used in the Phase 3 study.
39.	Are there adequate data supporting the waiver?			N/A
40.	Does the application include an IVIVC model?		X	The dosage form is immediate-release.
41.	Is information such as BCS classification mentioned, and supportive data provided?		X	
42.	Is information on mixing the product with foods or liquids included?		X	

43.	Is there any in *vivo* BA or BE information in the submission?		X	This is a 505(b)(1) NDA. OCP will review all BA/BE/PK studies.
FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
44.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
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
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
47.	Are there any potential review issues identified?	X		Refer to the Biopharmaceutics information request comments on page 3.

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

See appended electronic signature page}
Liang Zhou, Ph.D.
CMC Lead
(Reviewer, CMC of IQA)
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment

See appended electronic signature page}
Okpo Eradiri, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

See appended electronic signature page}
Ali Al-Hakim, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment

ATTACHMENT 1

INITIAL NDA RISK ASSESSMENT TABLE (Capsules). Table Completed by CMC Lead. Also see Foot Notes.

Product attribute/CQA	Factors that can impact the CQA	Probability* (O)	Severity of Effect* (S)	Detectability* (D)	FMECA RPN Number**	Comment	Risk***
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	4	2	Release and Stability (2)	8	12 months stability data provided.	L
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3 (b) (4)	2	3	18	Highly insoluble DS.	L
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	(b) (4)	3	3	36		M
Dissolution	• Formulation Container closure • Raw materials • Process parameters • Scale/equipment • Site	3	2	2	12	ONDQA Biopharmaceutics will assess it	L
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	1	2	3	6	OPS Micro will assess	L

Notes: * Range 1-5 (1-low, 5-high); **RPN#= O × S × D. *** RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125).
Source of the NDA RISK ASSESSMENT TABLE: From various presentations on OPQ reorganization.

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

FINAL NDA RISK ASSESSMENT TABLE

(To be completed by primary CMC and Biopharmaceutics Reviewers)

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	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L			
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M			
Dissolution	• Formulation Container closure • Raw materials • Process parameters • Scale/equipment • Site	L			
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			

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

/s/

OKPONANABOFA ERADIRI
09/23/2014

LIANG ZHOU
09/23/2014

ANGELICA DORANTES
09/23/2014

ALI H AL HAKIM
09/23/2014