

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203505Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: February 22, 2012

To: NDA 203-505

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 203-505, ospemifene oral tablet, 60 mg, Osphena™. Ospemifene is a new molecular entity (NME).

I have assessed the ONDQA reviews of NDA 203-505 by Hitesh Shroff, Ph.D. (Drug Substance and Drug Product) and Karen Riviere, Ph.D. (Biopharmaceutics).

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommendation of a drug product shelf life of 24 months for the proposed commercial product when stored at room temperature.

The initial ONDQA review was entered into DARRTS on December 12, 2012, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites acceptability and pending labeling issues. A separate Biopharmaceutics review was entered into DARRTS on December 11, 2012. The dissolution method and acceptance criterion were found to be acceptable.

All CMC related label/labeling issues were satisfactorily resolved through an amendment dated December 19, 2012. On January 24, 2013 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES. A second CMC review was entered into DARRTS on February 20, 2012 following the updating of the status of the recommendation from the Office of Compliance and resolution of the CMC related labeling issues.

A Method Validation Consult Request was generated to evaluate the test methods for Assay and Impurities for drug substance and drug product. The Method Validation Report Summary was entered into DARRTS on September 27, 2012, stating the methods are acceptable for quality control and regulatory purposes.

Osphena, ospemifene, tablets are white to off-white, oval, film-coated, biconvex tablets, with one side engraved "60". Osphena tablets contain 60 mg of active ingredient, ospemifene and the following inactive ingredients, pregelatinized starch, mannitol, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate. The tablets are coated [REDACTED] (b) (4). Osphena tablets are supplied in bottles and blisters to protect it from light and moisture.

Ospemifene is a white to off-white powder. Ospemifene is manufactured at (b) (4) and packaged at (b) (4). The detailed CMC related information for ospemifene is provided in DMF (b) (4). The manufacturer provided a letter of authorization to reference DMF (b) (4) in connection with NDA 203-505. The DMF (b) (4) was reviewed on December 12, 2012 and was found to be adequate.

Secondary reviews of the CMC reviews were performed by Moo-Jhong Rhee, Ph.D.
Secondary review of the Biopharmaceutics review was performed by Tapash Ghosh, Ph.D.

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

/s/

TERRANCE W OCHELTRIE
02/26/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 20, 2013

From: Hitesh Shroff, Ph.D.

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 203505

Subject: Final Recommendation

CMC review #1 noted the following pending issues:

1. The label/labeling issues were not resolved.
2. An overall "ACCEPTABLE" site recommendation was not made by the Office of Compliance for this application.

Because of the above deficiencies, this NDA was not recommended for approval from the ONDQA perspective.

Labeling revisions submitted 2/19/2013 have satisfactorily resolved all labeling deficiencies (see **Attachment -1**).

Also, the Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in the NDA (see **Attachment -2**).

Final Recommendation:

From the ONDQA perspective, this NDA is now recommended for "Approval" with an expiration dating period of 24 months.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment-2

EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA203505/000	Sponsor:	SHIONOGI INC
Org. Code:	580		300 CAMPUS DR STE 300
Priority:	14		FLORHAM PARK, NJ 07832
Stamp Date:	26-APR-2012	Brand Name:	OSPEMIFENE TABLETS
PDUFA Date:	26-FEB-2013	Estab. Name:	
Action Goal:		Generic Name:	OSPEMIFENE TABLETS
District Goal:	28-DEC-2012	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; OSPEMIFENE; 60MG
FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765
	H. SHROFF	Review Chemist	3017962116
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 24-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 21-MAY-2012	by EES_FROD		

Establishment:	(b) (4)	AADA:	
DMF No:		CAI Status:	NONE
Responsibilities:			
Profile:			
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-MAY-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b) (4)	AADA:	
DMF No:		CAI Status:	NONE
Responsibilities:			
Profile:			
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: (b) (4)

MF No: AADA:
Responsibilities:

Profile: OAI Status: NONE

1st Milestone: OC RECOMMENDATION
Milestone Date: 16-AUG-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

MF No: AADA:
Responsibilities:

Profile: OAI Status: NONE

1st Milestone: OC RECOMMENDATION
Milestone Date: 21-MAY-2012
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Establishment: CFN: 9614387 FEI: 1000370240
PENN PHARMACEUTICALS SERVICES LTD.

MF No: TREDEGAR, GWENT, WALES, GWENT, UNITED KINGDOM AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

1st Milestone: OC RECOMMENDATION
Milestone Date: 24-JAN-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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

/s/

HITESH N SHROFF
02/20/2013

MARIE KOWBLANSKY on behalf of MOO JHONG RHEE
02/20/2013

NDA 203505

 ^{(b) (4)} (ospemifene) tablets
60 mg

Shionogi, Inc.**Hitesh Shroff, Ph.D.**
Review Chemist**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV****CMC Review of NDA 203505
For the Division Reproductive and Urologic Products
(HFD-580)**

Table of Contents

Table of Contents	2
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product and Drug Substance.....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Not-Approval Recommendation.....	8
III. Administrative	9
A. Reviewer’s Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:	10
Body Of Data.....	10
S DRUG SUBSTANCE [Ospemifene, Shionogi, Inc.]	10
P DRUG PRODUCT [Ospemifene, tablets]	16
A APPENDICES	50
R REGIONAL INFORMATION	50
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	51
A. Labeling & Package Insert.....	51
B. Environmental Assessment Or Claim Of Categorical Exclusion	57
III. List of Deficiencies:	57
IV. Attachment	58

Chemistry Review Data Sheet

1. NDA 203505
2. REVIEW:#1
3. REVIEW DATE: 12-Dec-2012
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	26-Apr-2012
Amendment	14-Aug-2012
Amendment	24-Aug-2012
Amendment	03-Oct-2012

1. NAME & ADDRESS OF APPLICANT

Name: Shionogi, Inc.
Address: 300 Campus Drive
Florham park, NJ 07932

Representative: Ting Chen
Director, Regulatory Affairs
300 Campus Drive
Florham park, NJ 07932

Telephone: 906-966-6900
Email: tchen@shionogi.com

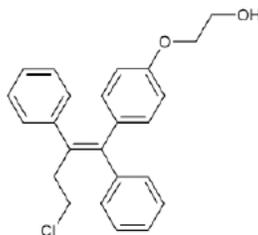
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Ospheña
- b) Non-Proprietary Name (USAN): Ospemifene
- b) Code Name/# (ONDQA only): None
- c) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1 (Ospemifene)
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Selective estrogen receptor modulator (SERM)

11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 60 mg Ospemifene
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:



Ospemifene

USAN Name:	Ospemifene
Chemical name:	Z-2-[4-(4-chloro-1,2-diphenylbut-1-enyl) phenoxy] ethanol Ethanol, 2-[4-(1Z)-4-chloro-1,2-diphenyl-1-butenyl] phenoxy]- 2[p-[(Z)-4-Chloro-1,2-diphenyl-1-butenyl] phenoxy] ethanol
CAS number:	128607-22-7
Molecular Formula:	C ₂₄ H ₂₃ ClO ₂
Molecular Weight:	378.9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
		(b) (4)	Ospemifene	1	Adequate	12-Dec-2012	(b) (4)
			(b) (4)	1	Adequate	12-Dec-2012	
				4	Adequate		
				4	Adequate		
				4	Adequate		
				4	Adequate		
				4	Adequate		

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: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Acceptable	11-Dec-2012	Kareen Riviere
LNC	N/A		
Methods Validation	Acceptable	26-Sep-2012	Michael L. Trehy
DMEPA	N/A		
EA	Claim for categorical exclusion submitted	April 26, 2012	Hitesh Shroff, CMC
Microbiology	N/A		

The Chemistry Review for NDA 203-505

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product.

However, the label/labeling issues are still *not* satisfactorily resolved.

Also, a site recommendation from the Office of Compliance has *not* been made as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval in its present form per 21 CFR 314.125(b)(6) and (13) until these pending issues are resolved.

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

No recommendations at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Substances

(b)(4) tablets contain 60 mg of active ingredient, ospemifene. Ospemifene is a white to off-white powder. Ospemifene is manufactured at (b)(4)

(b)(4) The detailed CMC related information for ospemifene is provided in DMF (b)(4) The manufacturer provided a letter of authorization to reference DMF (b)(4) in connection with NDA 203-505. The DMF (b)(4) was reviewed on 12-12-2012 and was found to be adequate.

(2) Drug Product

(b)(4) tablets are white to off-white, oval, film-coated, biconvex tablets, with one side engraved "60". (b)(4) tablets are supplied in bottles and blisters to protect it from light and moisture. (b)(4) tablets contain 60 mg of active ingredient, ospemifene and the following inactive ingredients, pregelatinized starch, mannitol, povidone, sodium starch

Executive Summary Section

glycolate, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate. The tablets are coated with (b) (4).

The manufacturing of (b) (4) tablets is performed using conventional manufacturing methods (b) (4).

Three primary stability batches containing approximately (b) (4) tablets were manufactured at Penn Pharmaceutical Services Ltd. in UK.

The proposed release specification of the finished product include appearance, identification, assay of the active ingredient, content uniformity, impurities, and microbial limits. The proposed specification are deemed adequate to assure the identity, strength, purity, and quality of the drug product.

Based on the stability data from three production scale batches of (b) (4) at long term (60 months) and accelerated (6 months) conditions, the proposed 24 months expiration dating period, when stored at room temperature, is granted.

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

Ospemifene is an estrogen receptor agonist/antagonist indicated for the treatment of vulvar and vaginal atrophy due to menopause. A typical dosage is one tablet per day taken with food. (b) (4) tablets are supplied in bottles and blisters.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(6)

- The label/labeling issues are still pending (see the **List of Deficiencies**, p. 57)

21 CFR 314.125 (b)(13)

- No overall "ACCEPTABLE" site recommendation has been made from the Office of Compliance for this application.

III. Administrative**A. Reviewer's Signature**

Hitesh Shroff, Ph.D./ 12-12-2012

B. Endorsement Block

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, Division 2

C. CC Block

Donna Christner, Ph.D.

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

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

/s/

HITESH N SHROFF
12/12/2012

MOO JHONG RHEE
12/12/2012
Chief, Branch IV

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

METHODS VALIDATION REPORT SUMMARY

TO: Hitesh Shroff, CMC Reviewer
Donna Christner, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: donna.christner@fda.hhs.gov or hitesh.shroff@fda.hhs.gov
Phone: (301) 796-1341 (Donna) or (301) 796-2116 (Hitesh)
Fax: (301) 796-9877

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: 203505

Name of Product: (b) (4) (ospemifene) tablets, 60 mg

Applicant: Shionogi, Inc.

Applicant's Contact Person: Ting Chen

Address: 300 Campus Drive, Florham Park, NJ 07932

Telephone: (973) 307-6900 Fax: (973) 966-2820

Date Methods Validation Consult Request Form Received by DPA: 6/25/12

Date Methods Validation Package Received by DPA: 6/25/12

Date Samples Received by DPA: 7/31/12

Date Analytical Completed by DPA: 9/26/12

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 memo for analyst's results and comments.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-2158

Date: September 26, 2012

To: Hitesh Shroff, Methods Validation Requestor, CMC Reviewer
Donna Christner, Methods Validation Requestor, CMC Lead

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)

From: Daniel J. Mans, Chemist (HFD-920)

Subject: Methods Validation for NDA 203505
(b) (4) (Ospemifene) tablets 60 mg
Shionogi, Inc.

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

1. Assay of ospemifene drug substance by high-performance liquid chromatography (b) (4) VR-04700E.
2. Impurities of ospemifene drug substance by high-performance liquid chromatography (b) (4) VR-04600E.
3. Assay of ospemifene tablets 60 mg following Shionogi, Inc. procedure 3.2.P.5.2.4
4. Purity of ospemifene tablets 60 mg following Shionogi, Inc. procedure 3.2.P.5.2.5
5. Dissolution of ospemifene tablets following Shionogi, Inc. procedure 3.2.P.5.2.7

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods.

1. Impurities of ospemifene drug substance by high-performance liquid chromatography (b) (4) VR-04600E.
 - VR-04600E procedure and % Impurities calculations were aided by Document Ref: METR-0524-AS (b) (4)
2. Dissolution of ospemifene tablets following Shionogi, Inc. procedure 3.2.P.5.2.7
 - For the Dissolution Calculation on page 8 a factor of 100 needs to be included in the equation to result in a percent value

Ospemifene Drug Substance HPLC Assay (VR-04700E)

Drug Substance 1 = (b) (4); Drug Substance 2 = 100.0%

Assay AVG = 100.1% (Acceptance Criteria: 97.0-103.0%)

Ospemifene Drug Substance Impurities by HPLC (VR-04600E)

(b) (4)
Total Impurities = (b) (4) (Acceptance Criteria NMT (b) (4))

Ospemifene Tablets 60 mg HPLC Assay (3.2.P.5.2.4)

Drug Product 1 = 60.9 mg / tablet; Drug Product 2 = 61.0 mg / tablet (Acceptance Criteria = 57.0 – 63.0 mg / tablet)

Ospemifene Tablets 60 mg Impurities by HPLC(3.2.P.5.2.5)

Total % Impurities = (b) (4) (Acceptance Criteria (b) (4))

RRT check on all Drug Substance and Drug Product impurities was close to reported values with the exception of (b) (4) which were slightly different from the reported values.

Dissolution of Ospemifene Drug Product (3.2.P.5.2.7)

AVG % tablet = (b) (4) (Acceptance Criteria $Q \geq$ (b) (4) @ 60 min.)

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

/s/

MICHAEL L TREHY
09/27/2012

BENJAMIN J WESTENBERGER
09/27/2012

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

METHODS VALIDATION CONSULT REQUEST FORM

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

FROM: Hitesh Shroff, Methods Validation Requestor, CMC Reviewer
Donna Christner, Methods Validation Requestor, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: donna.christner@fda.hhs.gov and/or hitesh.shroff@fda.hhs.gov
Phone: (301)-796-1341 (Donna) or 301-796-2116 (Hitesh)
Fax.: (301)-796-9877

Through: Moo-Jhong Rhee, Branch Chief
Phone: (301)-796-1440

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203505

Name of Product: (b) (4) (ospemifene) tablets, 60 mg

Applicant: Shionogi, Inc

Applicant's Contact Person: Ting Chen

Address: 300 Campus Drive, Florham Park, NJ 07932

Telephone: 973-307-6900 Fax: 973-966-2820

Date NDA Received by CDER: **4/26/2012**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **4/26/12**

Special Handling Required: No

DATE of Request: **June 21, 2012**

DEA Class: N/A

Requested Completion Date: **9/25/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **2/26/2013**

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.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 203505
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				NDA Section 3.2.P.5.1
Specifications/Methods for New Drug Substance(s)				DMF (b) (4); see scanned document
Specifications/Methods for Finished Dosage Form(s)				NDA Section 3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.				NDA Section 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				DMF (b) (4) and NDA Section 3.2.P.5.4
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
none provided	Drug Substance Assay	scanned document	0	DMF (b) (4), scanned method will be emailed separately
none provided	Drug Substance Related Substances/Impurities	scanned document	0	DMF (b) (4), scanned method will be emailed separately
none provided	Drug Product Assay	3.2.P.5.2.4	0	NDA in EDR
none provided	Drug Product Purity	3.2.P.5.2.5	0	NDA in EDR
none provided	Drug Product Dissolution Method	3.2.P.5.2.7	0	NDA is EDR

Additional Comments: Drug Substance information is contained in DMF (b) (4). Appropriate pages will be sent via email as a scanned PDF. Drug Product information is provided in NDA, which is in the EDR.

Dissolution method uses 2% SDS in dissolution media. Information on validation of Dissolution Method should also be provided to Kareen Riviere (Kareen.Riviere@fda.hhs.gov) and Sandra Suarez-Sharp (Sandra.suarez@fda.hhs.gov).

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

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

/s/

DONNA F CHRISTNER
06/22/2012

MOO JHONG RHEE
06/22/2012

JEANNIE C DAVID
06/25/2012
ONDQA Methods Validation Project Manager

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Reproductive and Urologic Products
NDA: 203505
Applicant: Shionogi Inc
Stamp Date: 26-Apr-2012
PDUFA Date: 26-Feb-2013
Trademark: TBD
Established Name: Ospemifene
Dosage Form: Tablet
Route of Administration: Oral
Indication: Treatment of vulvar and vaginal atrophy due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH) in post-menopausal women

CMC Lead: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

Summary and Critical Issues:

A. Summary

Ospemifene is a New Molecular Entity (NME). Ospemifene tablets contain 60 mg of ospemifene and are white to off-white, oval, film-coated, biconvex tablets with one side engraved "60". Tablets are packaged in two container closure configurations:

- HDPE bottles with CRC containing 100 tablets.
- (b) (4) push through blisters packaged in a cardboard blister card.
 - Physician samples of 15 tablets
 - Trade samples of 30 tablets

B. Critical issues for review

1. *The Drug Substance DMF will require review.*
2. *The specification appears to be in line with those set for solid oral dosage forms. The dissolution method included 2% SDS in the dissolution medium. Advice on dissolution*

was provided to the sponsor during the April 2011 by ONDQA BioPharm. Kareen Riviere has been assigned as the ONDQA BioPharm reviewer.

3. For the primary stability batches manufactured at Penn Pharma, 3 lots are packaged in bottles, but only two in blisters. In addition, one batch (in bottles only) has 60 months of stability, while the other two batches (in bottles and blisters) have only 6 months. Supporting stability data is provided on drug product manufactured at two different sites ((b)(4)) with real time data ranging from 36-60 months. The amount of data to be submitted was agreed to by the Agency in response to the August 2011 General Correspondence.

While the amount of stability data is atypical, it should be enough to decide on an expiry for tablets packaged in both bottles and blisters. The applicant had sought to move the primary manufacturing site from Penn Pharma to (b)(4) to be able to supply anticipated commercial demand. The applicant was advised to perform a BE study to bridge the two manufacturing sites. The results of the BE study, comparing Lot 0249A (PennPharma) to Lot 85518 (b)(4), did not show bioequivalence.

While the applicant reports that demand is not anticipated to require the larger manufacturing facility, since the manufacturing sites were not shown to manufacture equivalent tablets, the (b)(4) site could not be bridged to be used as the primary manufacturing site. However, it should be acceptable to use the stability data from both the (b)(4) sites as supporting data since developmental stability data from alternate manufacturing sites is typically accepted by the Agency without the need for demonstration of BE. Therefore, there should be adequate data on tablets packaged in both container closure configurations to allow adequate review to determine an expiration dating period in both container closure configurations. Updated information could also be requested by the primary reviewer during the review cycle if necessary.

C. Comments for 74-Day Letter

There are no comments to be conveyed at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Hitesh Shroff, Ph.D. is the assigned primary CMC reviewer. Kareen Riviere is the assigned ONDQA BioPharmaceutics reviewer.

REGULATORY BRIEFING RECOMMENDATION: As an NME, a Division Level Briefing is recommended, unless the review demonstrates that an Office Level briefing is warranted.

Donna F. Christner, Ph.D.

NDA Number: 203505 Type: 1

Established/Proper Name:
ospemifene

Applicant: Shionogi Letter Date: 26-Apr-2012

Stamp Date: 26-Apr-2012

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

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

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Attachment to the 356h
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.		X	N/A

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) 	X		Attachment to 356h
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) 	X		Attachment to 356h

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</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) 	X		Attachment to 356h
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		Attachment to 356h

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Claim for categorical exclusion as per 21 CFR 25.31(b). Calculated EIC of 0.0456 ppb

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF (b) (4) Specification also included in NDA.
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

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?	X		
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?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		Method Validation Request submitted to DARRTS on 22-Jun-2012

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

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?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Ospemifene	19-Dec-2011	Needs review
			(b) (4)	02-Dec-2011	No review found
	III			23-Dec-2011	Last review in 2007. May require review
				22-Feb-2012	No review found
	III			19-Oct-2011	No review found
	III			09-Dec-2011	No review found
	III			20-Dec-2011	No review found
					See ONDC Policies on Bottles and Blisters*

*Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
 Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

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

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

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Chief, Branch IV
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: <input checked="" type="checkbox"/> Yes; <input type="checkbox"/> No Review date: <u>23-Apr-2012</u>
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes <input type="checkbox"/> ; No <input checked="" type="checkbox"/> ; Maybe (please specify) _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial? _____
4) Is the nanomaterial a reformulation of a previously approved product? Yes <input type="checkbox"/> No <input type="checkbox"/>
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes <input type="checkbox"/> (Complete 8); No <input type="checkbox"/> (go to 9).
8) What is the reported particle size? Mean particle size _____; Size range distribution _____; Other _____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____ _____

REVIEW NOTES

Clinical studies were performed under IND 67,216 which was opened in 2003. The first CMC-related review filed to DARRTS was in 2008. The following is a brief overview of the CMC-related regulatory history.

Annual Report in 2008: Provided for an update to the CTD format. For Drug Substance, an alternate manufacturing site was added, specifications for Intermediate I assay and impurities were tightened and updated information on reference standards and stability data were also provided. For Drug Product, manufacturing and testing sites were changed, and dissolution data provided to support the change.

preNDA Meeting held 29-Sep-2009: The following CMC-related topics were discussed at the meeting:

- The Division agreed that the stability data presentation was adequate
- The Division agreed that the designation as starting materials of (b) (4) was appropriate, provided that:
 - Full information on the starting materials be provided either in the NDA or DMF
 - Only the listed manufacturers be used or if changes are made a prior approval supplement should be submitted
 - Specifications for the starting materials are established and related substances are listed as process impurities in the drug substance specification.

The sponsor disagreed with the amount of data requested for (b) (4), arguing that it was best designated as a reagent. The Division agreed to revisit this, and in a post-meeting comment stated that it should still be listed as a starting material since in provided a significant portion of the structure of the drug substance. However, since it is commercially available from a wide number of sources, the level of information required would be reduced. Specifications should be set and included in the related drug substance specifications as related substances, and an overview should be provided in the NDA concerning the commercial availability of (b) (4) as part of the justification for why additional information is not required.

- The sponsor requested advice concerning the design of the propose4d BE study and choice of tablet batches to be compared. CMC agreed (with ClinPharm) that the choice of batches was acceptable. ClinPharm provided advice on the design of the BE study.

Type C Guidance meeting held on 12-Apr-2011. Advice was sought concerning the BE study to support the manufacturing site change and on dissolution. Advice was provided by CMC, ClinPharm and ONDQA BioPharm. The following advice was provided:

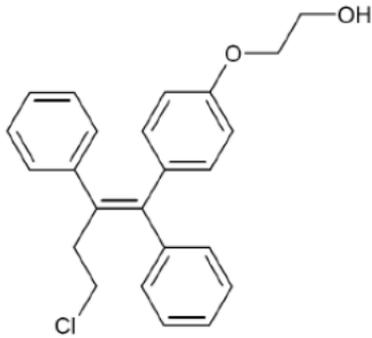
- The site change from Penn to (b) (4) involves Level 3 process changes and a BE study is required to bridge both the Penn 5 and (b) (4) 5 formulations to the proposed (b) (4) commercial formulation.
- The sponsor requested to submit 6 months of stability data on the registration lots of the commercial formulation and supportive data on 7 additional lots of 24 or more months, and then amend the NDA with an additional 3 months of stability data. The Division agreed it would be acceptable to submit the additional stability data at the 120-day safety date.

- The sponsor asked if the proposed dissolution method was acceptable. ONDQA BioPharm provided information on the dissolution report that should be included in the NDA
- The sponsor stated that (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] Additional information should be provided for evaluation.
- Sponsor stated that the one tablet to be used in the BE study would be 5 years old at the time of the study and asked if it was acceptable. The Division stated that if the tablets still met specifications, it was acceptable.

General Correspondence dated 18-Aug-2011. Sponsor stated that they are proposing to use Penn as the proposed manufacturer, instead of (b) (4) which changes the stability strategy. Sponsor proposed to submit the Original Penn 5 lot with 5 years of stability data, and then to manufacture two additional lots and submit 3 months of stability data at the time of filing, along with stability data from several (b) (4) lots. The Division recommended that each primary stability lot have at least 6 months of stability data upon submission and that additional data can be provided by month 5 of the review cycle.

DRUG SUBSTANCE:

Ospemifene is a New Molecular Entity. The majority of the information on the ospemifene drug substance is provided in DMF (b) (4), which will require review. The following information is provided in the NDA



Molecular Formula:

$C_{24}H_{23}O_2Cl$

Molecular Weight:

378.9 g/mol

Manufacturing

The name, address and responsibility of each facility in the manufacture and testing of the drug substance are provided below.



Comment: EES was submitted on 21-May-2012 by Rebecca McKnight. See Appendix 1 for full site information.

The specification for ospemifene is provided in Table 1.

Table 1. Drug Substance Specification for Ospemifene

Attribute	Method	Specification
Appearance	Visual	White to off-white, crystalline powder
Identification		
<ul style="list-style-type: none"> • Identification A 	IR	Spectrum must correspond to that of the standard
<ul style="list-style-type: none"> • Identification B 	UV	Spectrum must correspond to that of the standard
Assay (dried basis)	HPLC	97.0 – 103.0%
Impurities	HPLC	(b) (4)
Particle Size Distribution	Laser diffraction	(b) (4)
Residual Solvents	GC	
<ul style="list-style-type: none"> • (b) (4) 		(b) (4)
Loss on Drying	USP <731>	
Heavy Metals	USP <231> Method II	
Residue on Ignition	USP <281>	
Microbial Limits	USP <61>	
(b) (4)		(b) (4)
(b) (4)		

Comment: The DMF will require review.

DRUG PRODUCT

Ospemifene tablets contain 60 mg of ospemifene and are white to off-white, oval, film-coated, biconvex tablets with one side engraved “60”. Tablets are packaged in two container closure configurations:

- HDPE bottles with (b) (4) containing 100 tablets.
- (b) (4) push through blisters packaged in a cardboard blister card.
 - Physician samples of 15 tablets
 - Trade samples of 30 tablets

Tablets have the following formulation:

Table 1. Composition of Ospemifene Tablets

Component	Quantity/Tablet (mg)	Function	Quality Standard
Ospemifene	60.0	Active	In-house
Pregelatinized starch (b) (4)	(b) (4)	(b) (4)	NF
Mannitol			USP
Povidone (b) (4)			USP
Sodium starch glycolate			NF
Microcrystalline cellulose (b) (4)			NF
Colloidal silicon dioxide (b) (4)			NF
Magnesium stearate			NF
(b) (4)			In-house
(b) (4)			USP
(b) (4)			(b) (4)



Tablet Formulations

A Phase II Dose-Ranging Study 15-50717 was performed using 5 mg, 15 mg and 30 mg tablets with a placebo. The 30 mg and 60 mg tablet formulations and placebo were used in clinical phase III studies. Tablet formulations used in clinical studies are presented in Table 3. The composition of the 60 mg tablets is the same as proposed for marketing.

Table 3. Components of Ospemifene Film-coated Tablets 5, 15, 30, 60 mg and Placebo used for Clinical Studies

Formulation	5 mg film-coated tablet	15 mg film-coated tablet	30 mg film-coated tablet	60 mg film-coated tablet	Placebo film-coated tablet
Lot Number(s) (Manufacturer(s))	A07005 (b) (4)	0247A (Penn)	0248A (Penn)	0107-852, 0208-915 (b) (4) 0249A (Penn), A07006, A10016, A10017, A10018, A10019, 85481, 85518, (b) (4)	0246A (Penn) 85207 (b) (4)
Components					
Core:					
Ospemifene	5.0 mg	15.0 mg	30.0 mg	60.0 mg	--
Lactose monohydrate	(b) (4)				
Pregelatinized starch					
Mannitol					
Povidone					
Sodium starch glycolate					
Microcrystalline cellulose					
Colloidal silicone dioxide					
Magnesium stearate					
(b) (4)					
(b) (4)					
(b) (4)	(b) (4)				

Penn: Penn Pharmaceutical Services

Table 1. Batch History – Clinical and Primary Stability Batches

	002 (30 mg capsule)	0107-852 ¹ (60 mg tablet)	0249A (60 mg tablet)	A07006 (60 mg Tablet)	004019 (60 mg tablet)	004021 (60 mg tablet)
Use of Batch	BE Study (capsule vs. tablet) ²	Multiple clinical studies including BE between tablet and capsule ²	Multiple clinical studies /Registration lot/Primary stability ²	Multiple clinical studies ²	Registration lot/Primary stability	Registration lot/Primary stability
DP Mfg. Site	(b) (4)		Penn Pharma	(b) (4)	Penn Pharma	Penn Pharma
Batch Size	(b) (4)		(b) (4)	(b) (4)	(b) (4)	
Drug Substance Lot	99E27	00E21	1052557	1052557	1389948	1389953
Date of Manufacture	October 1999	July 2001	September 2005	June 2007	September 2011	September 2011

¹ (b) (4)

² Refer to 3.2.P.2.2 for a complete description of all clinical studies the drug product batches were used in.

(b) (4)

Penn Pharma: Penn Pharmaceutical Services, UK

MANUFACTURE

The name, address and responsibility of each manufacturer involved in manufacturing and testing the drug product are provided.

Manufacturer(s)	Responsibilities
Penn Pharmaceutical Services Ltd 23-24 Tafarnaubach Industrial Estate Tredegar, Gwent, South Wales NP22 3AA United Kingdom Establishment number: 1000370240	Manufacture, Primary Packaging, Labeling, Testing, Release and Stability
(b) (4)	

Comment: EES was submitted on 21-May-2012 by Rebecca McKnight. See Appendix 1 for full site information.

The tablets are manufactured according to the following flow chart. A narrative is also provided.

Figure 1. Process Flow Diagram



Comment: *The Pharmaceutical Development report details the thinking behind the final manufacturing process. However, there is no detailed discussion of Quality by Design factors. Information is adequate to allow review.*

SPECIFICATION

The quality of the drug product is controlled by adherence to the following specification:

Table 1. Specifications

Test Items	Methods	Release Criteria	Shelf Life Criteria
Description	Visual	White to off-white, oval, film-coated, biconvex tablets, one side engraved "60"	White to off-white, oval, film-coated, biconvex tablets, one side engraved "60"
Identification	HPLC	Positive	--
Identification	UV	Positive	--
Assay	HPLC	54.0 – 66.0 mg/tablet (90.0%-110.0%)	54.0 – 66.0 mg/tablet (90.0%-110.0%)
Purity	HPLC		(b) (4)
Uniformity of Dosage Units: Content Uniformity	USP <905>	Complies	--
Dissolution	USP <711>	Q ≥ (b) (4) at 60 min.	Q ≥ (b) (4) at 60 min. (b) (4)
Microbiological Quality	USP <61> & <62>		(b) (4)
		(b) (4)	

Comment: The specification appear to be in line with those set for solid oral dosage forms. The dissolution method included 2% SDS in the dissolution medium. Advice on dissolution was provided to the sponsor during the April 2011 by ONDQA BioPharm. Kareen Riviere has been assigned as the ONDQA BioPharm reviewer.

STABILITY

The applicant requests 24 month expiration dating period based on the following stability package. The shaded rows are the primary stability batches.

Table 1. Stability Study Summary

Drug Product Batches	Manufacturer	Batch size	Container closures	Stability Data (months)		
				40°C/75%RH	25°C/60%RH	
0249A	Penn Pharma	(b) (4)	HDPE Bottle	0, 1, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36, 48, 60	
004019	Penn Pharma		HDPE Bottle and Blister	0, 1, 3, 6	0, 1, 3, 6	
004021	Penn Pharma		HDPE Bottle and Blister	0, 1, 3, 6	0, 1, 3, 6	
0107-852	(b) (4)		HDPE Bottle	0, 1, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36, 48, 60	
0107-853			HDPE Bottle	0, 1, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36, 48, 60	
0208-915			HDPE Bottle	0, 1, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36, 48, 60	
A07006			HDPE Bottle	0, 1, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36, 48	
85481 ³			HDPE Bottle and Blister	0, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36	
85509 ³			HDPE Bottle and Blister	0, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36	
85518 ³			HDPE Bottle and Blister	0, 3, 6	0, 1, 3, 6, 9, 12, 18, 24, 36	
			(b) (4)			

³ Testing for the 30°C/65% RH storage condition was performed; no out of specification or out of trend results were obtained at the 40°C/75% RH time points.

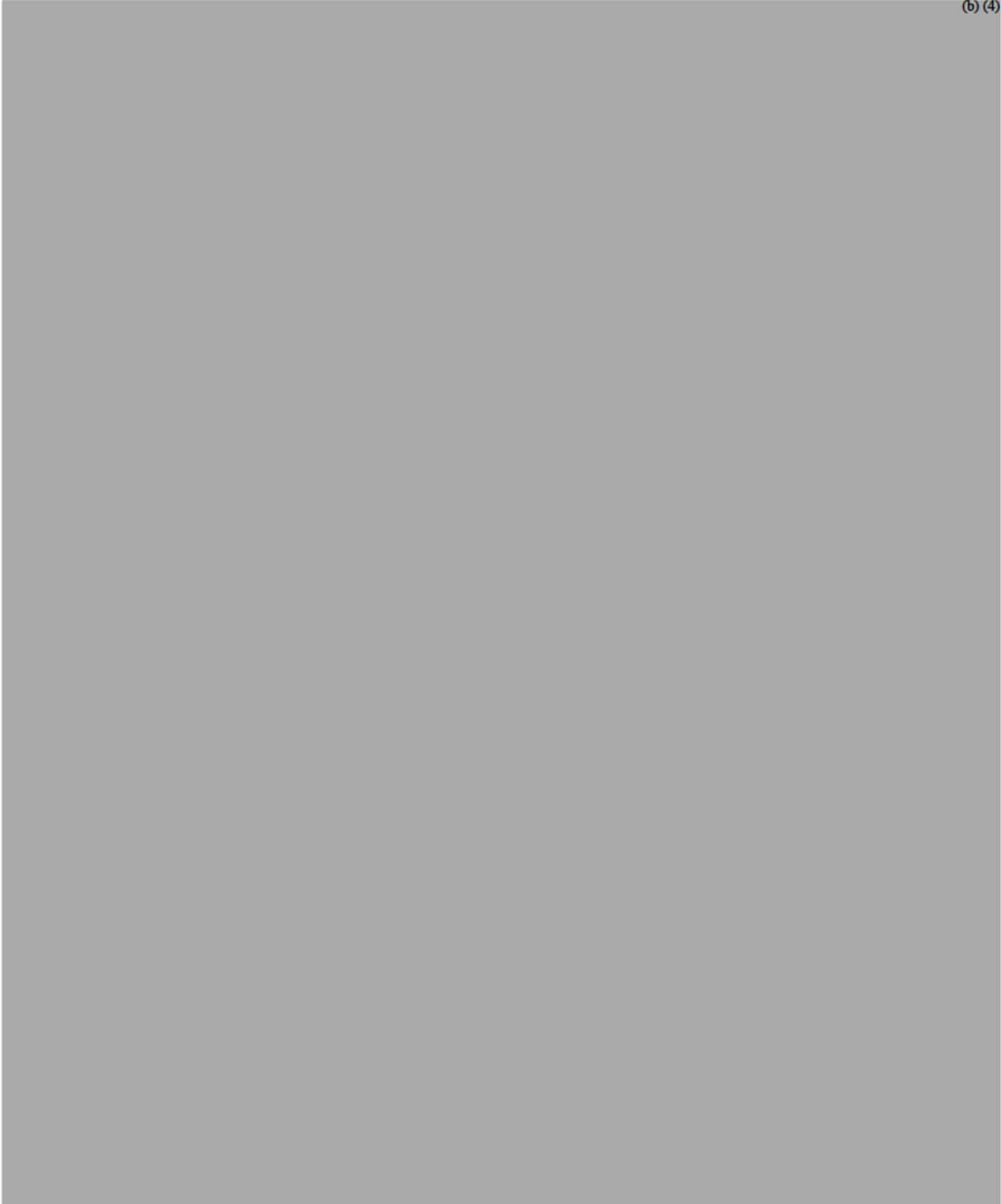
Comment: For the primary stability batches manufactured at Penn Pharma, 3 lots are packaged in bottles, but only two in blisters. In addition, one batch (in bottles only) has 60 months of stability, while the other two batches (in bottles and blisters) have only 6 months. Supporting stability data is provided on drug product manufactured at two different sites (b) (4) sites) with real time data ranging from 36-60 months. The amount of data to be submitted was agreed to by the Agency in response to the August 2011 General Correspondence.

While the amount of stability data is atypical, it should be enough to decide on an expiry for tablets packaged in both bottles and blisters. The applicant had sought to move the primary manufacturing site from Penn Pharma to (b) (4) to be able to supply anticipated commercial demand. The applicant was advised to perform a BE study to bridge the two manufacturing sites. The results of the BE study, comparing Lot 0249A (PennPharma) to Lot 85518 (b) (4) did not show bioequivalence.

While the applicant reports that demand is not anticipated to require the larger manufacturing facility, since the manufacturing sites were not shown to manufacture equivalent tablets, the (b) (4) site could not be bridged to be used as the primary manufacturing site. However, it should be acceptable to use the stability data from both the (b) (4) sites as supporting data since developmental stability data from alternate manufacturing sites is typically accepted by the Agency without the need for demonstration of BE. Therefore, there should be adequate data on tablets packaged in both container closure configurations to allow adequate review to determine an expiration dating period in both container closure configurations. Updated information could also be requested by the primary reviewer during the review cycle if necessary.

APPENDIX 1

(b) (4)



Manufacturer:	Penn Pharmaceutical Services Ltd
Address:	23-24 Tafarnaubach Industrial Estate Tredegar, Gwent, South Wales NP22 3AA United Kingdom
Site Contact	David Sanson Director, Quality Phone: +44 (0) 1495 713699 Mobile: (b) (6) Email: david.sanson@pennpharm.com
FDA Establishment Identifier (FEI)	Establishment number: 1000370240
Responsibility:	Manufacture, Release and Stability Testing of Drug Product

Manufacturer:	(b) (4)
Address:	
Site Contact	
FDA Establishment Identifier (FEI)	
Responsibility:	

All facilities are ready for inspection. Please note, we anticipate completion of drug product process validation activities by the end of September 2012.

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

/s/

DONNA F CHRISTNER
06/22/2012

MOO JHONG RHEE
06/22/2012
Chief, Branch IV