

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203505Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203505

SUPPL #

HFD # 580

Trade Name Osphena

Generic Name ospemifene

Applicant Name Shionogi Inc.

Approval Date, If Known February 26, 2013

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 067216                      YES                       ! NO   
! Explain:

Investigation #2  
IND # 067216                      YES                       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: George Lyght, Pharm.D  
Title: Sr. Regulatory Health Project Manager  
Date: Feb 26, 2013

Name of Office/Division Director signing form: Victoria Kusiak, M.D.  
Title: Deputy Director, ODE III

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEORGE A LYGHT  
02/26/2013

VICTORIA KUSIAK  
02/26/2013

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 203505

Supplement Number: \_\_\_\_\_

NDA Supplement Type (e.g. SE5):  
\_\_\_\_\_

Division Name: Division of  
Reproductive and Urologic  
Products

PDUFA Goal Date: Feb 26,  
2013

Stamp Date: 4/26/2012

Proprietary Name: Osphena

Established/Generic Name: ospemifene

Dosage Form: Tablets

Applicant/Sponsor: Shionogi Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) The treatment of vulvar and vaginal atrophy

(2) \_\_\_\_\_

(3) \_\_\_\_\_

(4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** The treatment of vulvar and vaginal atrophy

**Q1:** Is this application in response to a PREA PMR?

Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_

Supplement #: \_\_\_\_\_

PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

*additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEORGE A LYGHT  
11/26/2012

## Debarment certification statement

Shionogi Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application for **Ospemifene**.

  
\_\_\_\_\_  
Ting Chen, M.S.  
Director, Regulatory Affairs

17 April 2012

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203505 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Osphe <sup>a</sup> Established/Proper Name: ospemifene Dosage Form: tablets		Applicant: Shionogi Inc. Agent for Applicant (if applicable):
RPM: George Lyght, PharmD		Division: Division of Reproductive & Urologic Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)            Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>February 26, 2013</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC       </p> <p>         NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)          Subpart I <input type="checkbox"/> Approval based on animal studies       </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request       </p> <p>         BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)          Subpart H <input type="checkbox"/> Approval based on animal studies       </p> <p>         REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required       </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Yes
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 2-26-13
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Yes
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Yes
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	2-25-13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	4-26-12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	1-24-13
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 12-17-12 & 2-20-13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 2-14 & 2-23-13 <input checked="" type="checkbox"/> ODPD (DDMAC) 2-19 & 2-22-13 <input checked="" type="checkbox"/> SEALD 2-22-13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	7-5-12
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>12-5-12</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg Sept. 29, 2009
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg Oct. 4, 2005
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2-26-13
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2-25-13
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	2-8-13
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Clin Review page 17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None IRT QT Study Review 1-15-13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 2-12-13
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 2-12-13
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 1-12-12 , 2-22-13 & 2-26-13
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 1-12-12 & 2-22-13 & 2-26-13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 1-15-13
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 1-15-13
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None IND 067216/ -9-8-05 3-8-07, 5-7-07 & 8-25-08/ NDA 203505/ -1-15-13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc 12-3-12
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 11-30-12 Included in P/T review, page71
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 2-26-13
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 2-20-13
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 12-12-12 & 2-20-13
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None ONDQA/Biopharm 12-11-2012

❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )		12-12-12 (CMC review p. 57)
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )		
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )		Date completed: 1-24-13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )		<input checked="" type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEORGE A LYGHT  
02/28/2013



NDA 203505

**INFORMATION REQUEST**

**From:** Lyght, George  
**Sent:** Tuesday, February 19, 2013 11:46 AM  
**To:** 'Chen, Ting'  
**Subject:** Ospheña PPI

Hi Ting,

Here is the PPI Labeling for you to review and return as soon as possible. Please acknowledge that you have received it.

Thanks,  
George



ospemifene  
(sphená) DMPP PPI



ospemifene  
(sphená) 203505 DM

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/s/  
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GEORGE A LYGHT  
02/19/2013



NDA 203505

**INFORMATION REQUEST**

**From:** Chen, Ting [mailto:tchen@shionogi.com]  
**Sent:** Friday, February 15, 2013 9:09 AM  
**To:** Lyght, George  
**Subject:** RE: Updated Osphena labeling

Dear George,

Yes, Got it. Many thanks,

Best regards,

Ting

**From:** Lyght, George [mailto:George.Lyght@fda.hhs.gov]  
**Sent:** Friday, February 15, 2013 8:46 AM  
**To:** Chen, Ting  
**Subject:** Updated Osphena labeling

Hi Ting,

We have updated the labeling and request that you use this version to re-submit. Please reply that you have received this version.

Thanks.

Regards,  
George

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GEORGE A LYGHT  
02/19/2013



NDA 203505

**LABELING PMR/PMC DISCUSSION COMMENTS**

Shionogi Inc.  
Attention: Ting Chen, M.S.  
Director, Regulatory Affairs  
300 Campus Drive  
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your April 26, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Osphe<sup>na</sup> oral tablets 60 mg.

We also refer to our July 9, 2012, letter in which we notified you of our target date of January 8, 2013, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On April 26, 2012, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We will be sending other proposed changes as we continue our review. Additionally, we have the following comments:

We recommend that you implement the following revisions -

*A. General Comments for Container Labels and Carton Labeling*

1. Ensure the established name is presented in a font and prominence that is ½ the size of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features so that it is in accordance with 21 CFR 201.10(g)(2).
2. Remove the word (b) (4) from the dosage form statement ( (b) (4) ) to be consistent with the presentation of the dosage form presentation in the insert labeling. The revised presentation would appear as:

**Osphe<sup>na</sup>**  
(ospemifene) tablets  
60 mg

*B. Container Label (100 count)*

1. To improve readability, revise the proprietary name to title case, with only the first letter capitalized, 'Osphe<sup>na</sup>'. Words set in upper and lower case form

recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

2. Decrease the prominence of the company logo on the principal display panel to ensure it does not compete with the proprietary name and product strength. Additionally, reducing the prominence of the company logo will allow for more space to be used for prominent display of the warning statement 'For oral use only'.

C. *Blister Carton Labeling (15-count sample and 30-count trade)*

1. 30-count trade only: include the statement 'Two blister cards of 15 tablets each' under the quantity statement to improve clarity. The revised presentation may appear as follows:

'30 tablets  
(Two blister cards of 15 tablets)'

2. Revise the statement (b) (4) to read as follows to improve the clarity of the statement: 'Take one tablet orally (by mouth) once daily with food'. Additionally, ensure this statement appears on all blister labels.
3. Delete or reduce the prominence of the graphic that appears above the proprietary name as well as across the blister carton labeling. As currently presented, the graphic distracts attention from the proprietary name, established name, product strength, and newly added warning statement 'For oral use only'.

If you have any questions, call George Lyght, Pharm.D., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph, M.P.A.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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GEORGE A LYGHT  
01/08/2013  
Signing for Margaret Kober

Executive CAC

Date of Meeting: November 27, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Lynnda Reid, Ph.D., DRUP, Alternate Member  
Jeffrey Bray, Ph.D., DRUP, Reviewer  
Alex Jordan, Ph.D., DRUP Team Leader

Author of Draft: Jeffrey Bray, Ph.D.

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

NDA #203-505

Drug Name: Ospemifene

Sponsor: Shionogi, Inc.

**Background:** Ospemifene is a mixed estrogen agonist/antagonist (SERM) developed for treatment of vulvar and vaginal atrophy in postmenopausal women. The carcinogenicity study protocols were concurred with by eCAC on October 19, 2006. Ospemifene was considered to be non-genotoxic based on a battery of in vitro and in vivo studies.

#### **Rat Carcinogenicity Study**

Han Wistar rats (50/sex/group) were dosed with 10, 50, and 300 mg/kg/d in corn oil, with the high dose based on MFD. Dual control groups were used, each with 50 /sex/group. Markedly lower body weight was observed in all treated groups relative to controls for males and for females. Survival was significantly increased in all treated groups compared to control ranging from 86% to 96% for males compared to 68% and 74% for controls and 82% to 92% for females compared to 72% and 58% for controls. Exposure based on AUC at termination did not achieve very high multiples of the clinical exposure at the proposed dose (30%, 60%, and 125%), but this was expected.

There were significantly increased incidences of neoplasms in liver and thymus compared to control and above historical control incidence rates. In general, neoplastic findings are consistent with the known pharmacologic effects of a mixed estrogen agonist/antagonist on cell types that express the estrogen receptor.

## Liver and Thymus Neoplastic Findings in Rats at Necropsy during the 2-Year Oral Ospemifene Carcinogenicity Study

		Incidence of liver tumours: liver									
		Males					Females				
Tissue and finding	Level (mg/kg/day)	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Liver	No. examined:	50	50	50	50	50	50	50	50	50	50
hepatocellular adenoma	Finding present	0	2	3	2	0	0	1	4	4	0
hepatocellular carcinoma	Finding present	0	0	0	1	0	0	0	2	0	0
hepatocellular tumours combined		0	2	3*	3*	0	0	1	6**	4*	0

Key: Statistical analysis: \* = P<0.05, \*\* = P<0.01

		Incidence of thymic tumours: thymus									
		Males					Females				
Tissue and finding	Level (mg/kg/day)	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Thymus	No. examined:	50	50	48	49	48	49	49	49	49	50
benign thymoma	Finding present	0	5	8	9	0	3	10	21	11	2
malignant thymoma	Finding present	0	0	0	0	0	0	0	0	2	0
thymus epithelial tumours combined		0	5**	8***	9***	0	3	10*	21***	13**	2

Key: Statistical analysis: \* = P<0.05, \*\* = P<0.01, \*\*\* = P<0.001

*(Excerpted from Applicant's package)*

### Mouse Carcinogenicity Study

CD-1 mice (51/sex/group) were dosed with 100, 400, and 1500 mg/kg/d in corn oil, with the high dose based on MFD. Dual control groups were used, each with 51/sex/group. No significant treatment-related effect on body weight or survival was noted in females, except a lower relative body weight at the mid dose. The exposure based on AUC at termination did not achieve very high multiples of the clinical exposure at the proposed dose (2x, 4x, and 5x). However, this appears to be caused by a time-dependent decrease in exposure at all doses between weeks 13 and 52.

Female mice had significant treatment-related increases in adrenal and ovary neoplasms; the ovary neoplasms were without a dose relationship. The incidences of adrenal and ovarian neoplasms were above maximum historical control rates for female CD-1 mice. Liver and pituitary neoplasms showed a statistical increase compared to concurrent controls, but were within historical control incident rates. In general, neoplastic findings are consistent with the known pharmacologic effects of a mixed estrogen agonist/antagonist on cell types that express the estrogen receptor.

Males were terminated early (by week 24) with eCAC concurrence. Treatment-related morbidity due to urogenital swelling (inguinal hernias) was observed at all dose groups. This was determined to be an age-related phenomenon with younger males more susceptible to this effect.

**Table - Adrenal and Ovary Neoplastic Findings in Female Mice at Necropsy during a 2-Year Oral Ospemifene Carcinogenicity Study**

Incidence of neoplastic lesions: adrenal gland											
Tissue and finding	Level (mg/kg/day)	Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
		0	100	400	1500	0	0	100	400	1500	0
Adrenal gland subcapsular cell tumour	No. examined:	-	-	-	-	-	51	51	51	51	51
	Grade	-	-	-	-	-	51	51	50	47	51
	+	-	-	-	-	-	0	0	1	4	0
cortical adenoma	Grade	-	-	-	-	-	51	51	51	50	51
	+	-	-	-	-	-	0	0	0	1	0
	Grade	-	-	-	-	-	51	51	51	49	51
cortical carcinoma	+	-	-	-	-	-	0	0	0	2	0

Key: "-" = finding not present, "+" = finding present

Incidence of neoplastic lesions: ovary											
Tissue and finding	Level (mg/kg/day)	Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
		0	100	400	1500	0	0	100	400	1500	0
Ovary Benign sex cord stromal tumour	No. examined:	-	-	-	-	-	51	51	51	51	51
	Grade	-	-	-	-	-	50	43	38	38	50
	+	-	-	-	-	-	1	8	13	13	1
malignant sex cord stromal tumour	Grade	-	-	-	-	-	51	50	50	49	51
	+	-	-	-	-	-	0	1	1	2	0
	Grade	-	-	-	-	-	51	49	45	49	51
tubulostromal adenoma	+	-	-	-	-	-	0	2	6	2	0
	Grade	-	-	-	-	-	51	51	49	51	51
	+	-	-	-	-	-	0	0	2	0	0
tubulostromal carcinoma	Grade	-	-	-	-	-	51	50	51	48	51
	+	-	-	-	-	-	0	1	0	3	0
	Grade	-	-	-	-	-	51	51	48	50	51
Benign granulosa cell tumour	+	-	-	-	-	-	0	0	3	1	0
	Grade	-	-	-	-	-	49	41	47	47	48
	+	-	-	-	-	-	2	10	4	4	3
malignant granulosa cell Tumour	Grade	-	-	-	-	-	51	51	46	50	51
	+	-	-	-	-	-	0	0	5	1	0
	Grade	-	-	-	-	-	51	51	46	50	51
Benign luteoma	+	-	-	-	-	-	0	0	5	1	0
	Grade	-	-	-	-	-	51	51	46	50	51
	+	-	-	-	-	-	0	0	5	1	0
malignant luteoma	Grade	-	-	-	-	-	51	51	46	50	51
	+	-	-	-	-	-	0	0	5	1	0
	Grade	-	-	-	-	-	51	51	46	50	51
+	-	-	-	-	-	0	0	5	1	0	

Key: "-" = finding not present, "+" = present

*(Excerpted from Applicant's package)*

**Executive CAC Recommendations and Conclusions:**

Rat:

The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

The following were considered to be drug-related neoplasms in rats:

- **Liver** – benign and malignant hepatocellular neoplasms in females.
- **Thymus** – benign thymoma in both sexes and malignant thymoma in females.

Mouse:

The Committee agreed that the study in females was adequate, noting prior Exec CAC agreement with the protocol.

The following neoplasms were considered to be drug related in female mice:

- **Ovary**- benign and malignant tubulostromal tumors, sex-cord stromal tumors, granulosa-cell tumors, and luteal tumors
- **Adrenal**- subcapsular adenomas at the mid dose and high dose, cortical adenomas and carcinomas in females at the high dose.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\n  
/Division File, DRUP  
/Alex Jordan, DRUP  
/Jeffrey Bray, DRUP  
/George Lyght, DRUP  
/ASeifried, OND IO

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ADELE S SEIFRIED  
11/30/2012

DAVID JACOBSON KRAM  
11/30/2012



NDA 203505

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Shionogi Inc.  
300 Campus Drive  
Florham Park, NJ 07932

ATTENTION: Ting Chen, M.S.  
Director, Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated April 25, 2012, and received April 26, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ospemifene Tablets 60 mg.

We also refer to your correspondence, dated and received on June 20, 2012, requesting review of your proposed proprietary name, Osphe<sup>na</sup>. We have completed our review of the proposed proprietary name Osphe<sup>na</sup>, and have concluded that it is acceptable.

The proposed proprietary name, Osphe<sup>na</sup>, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If **any** of the proposed product characteristics as stated in your June 20, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Marcus Cato, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, George Lyght at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
09/14/2012

## INFORMATION REQUEST

Date: August 17, 2012

NDA 203505

Applicant: Shionogi Inc.

Regulatory Agent: Ting Chen, M.S.

FDA requestor: Jeffrey Bray

Type: Phone call and email

Dear Ms. Chen,

We have the following Information Request.

Provide the conducting laboratory Historical Control data for neoplasm types and incidences observed in mouse and rat 2-year carcinogenicity studies.

Thank you,

Maria Wasilik

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/s/  
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MARIA R WASILIK  
08/17/2012



NDA 203505

## INFORMATION REQUEST

Shionogi Inc.  
Attention: Ting Chen, M.S.  
Director, Regulatory Affairs  
300 Campus Drive  
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ospemifene oral tablets 60 mg.

We are reviewing your submission and have the following comments and information requests. We request a written response within 2 weeks in order to continue our evaluation of your NDA.

- Submit the results from the renal impairment study using the new classification scheme of renal impairment as described in FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010).
- Submit the population PK (PPK) and PPK/PD datasets and their corresponding analysis codes:
  - All datasets used for model development and PPK/PD analyses should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
  - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
  - If applicable, a model development decision tree and/or table which gives an overview of modeling steps.

As we continue to review the application, we may have additional information requests.

If you have any questions, call George Lyght, R.Ph., PharmD, Sr. Regulatory Project Manager, at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Margaret M. Kober, R.Ph., M.P.A.  
Chief Project Management Staff  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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MARGARET M KOBER  
08/07/2012  
Chief, Project Management Staff



NDA 203505

**METHODS VALIDATION  
MATERIALS RECEIVED**

Shionogi, Inc.  
Attention: Ting Chen  
300 Campus Drive  
Florham Park, NJ 07932

Dear Ting Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (ospemifene) tablets, 60 mg and to our June 26, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 31, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
07/31/2012



NDA 203505

**FILING COMMUNICATION**

Shionogi Inc.  
Attention: Ting Chen, M.S.  
Director, Regulatory Affairs  
300 Campus Drive  
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated April 26, 2012, received April 26, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ospemifene oral tablets 60 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 26, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 8, 2013.

During our filing review of your application, we identified the following potential review issues:

**Clinical:**

The primary efficacy analyses reported in the individual final study reports for 12-week Study 15-50310 and 12-week Study 15-50821 are not based on subjects who met all three baseline inclusion criteria: vaginal pH greater than 5, less than 5% superficial cells on a vaginal smear, and a most bothersome moderate to severe vaginal symptom. We will make our determination of efficacy based on demonstration of statistically significant improvement vs. placebo in the

recommended co-primary endpoints [most bothersome moderate to severe symptom (e.g. vaginal dryness and dyspareunia), vaginal pH and superficial and parbasal vaginal cells) for those subjects who met the three baseline criteria for a trial of treatment of the symptoms of vulvar and vaginal atrophy. The analyses reported in the application in the “Summary of Clinical Efficacy” document and the “Integrated Summary of Efficacy” document, however, appear to be based on subjects meeting all three of the recommended baseline inclusion criteria. The analyses presented in all documents should be consistent and, as stated, should be based on those subjects meeting all three of the recommended baseline inclusion criteria [a most bothersome moderate to severe vaginal symptom (consistent with the symptom to be analyzed), vaginal pH greater than 5 and less than 5% superficial cells on a vaginal smear].

Submit an addendum to the final study reports for Study 15-50310 and Study 15-50821 with the correct primary analyses (including only subjects who meet all three recommended baseline inclusion criteria) that are consistent with those presented in the “Summary of Clinical Efficacy” and the “Integrated Summary of Efficacy.”

**Biopharmaceutical:**

1. There is insufficient data to support the adequacy of the proposed dissolution method (e.g. selected dissolution medium and surfactant are not justified). Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
  - a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.
  - b. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm$  10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.
2. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for your proposed product.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The labeling for review should not include a header.
2. The labeling for review should only include approved proprietary and established drug names.
3. At the beginning of Section 17:

**Patient Counseling Information**

Use the following statement -

- "See FDA-approved patient labeling (Patient Information)"

We request that you resubmit labeling that addresses these issues by July 30, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call George Lyght, R.Ph., PharmD, Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Audrey Gassman, M.D.  
Acting Deputy Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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AUDREY L GASSMAN  
07/09/2012



NDA 203505

**PROPRIETARY NAME  
REQUEST WITHDRAWN**

Shionogi Inc.  
300 Campus Drive  
Florham Park, NJ 07932

Attention: Ting Chen, M.S.  
Director Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated April 25, 2012, received April 26, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ospemifene Tablets 60 mg.

Please also refer to your correspondence, dated and received April 26, 2012, requesting review of the proposed proprietary name (b) (4) for this drug product.

We acknowledge your correspondence dated and received June 20, 2012 notifying us that you are withdrawing your April 26, 2012 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of June 20, 2012.

We also acknowledge your new request for review of a proposed proprietary name in your correspondence dated and received June 20, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, George Lyght at 301-796-0948.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk  
Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
07/05/2012



NDA 203505

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Shionogi, Inc.  
Attention: Ting Chen  
300 Campus Drive  
Florham Park, NJ 07932

Dear Ting Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (ospemifene) tablets, 60 mg.

We will be performing methods validation studies on (b) (4) (ospemifene) tablets, 60 mg, and Ospemifene drug substance as described in NDA 203505.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

Drug substance assay and related substances/impurities  
Drug product assay, purity, and dissolution method

**Samples and Reference Standards**

100 (b) (4) (ospemifene) tablets, 60 mg  
500 mg Ospemifene reference standard  
200 mg Ospemifene drug substance (FC-1271a)  
50 mg Impurity A



**Equipment**

1 Waters Symmetry C<sub>18</sub>, 4.6 x 150 mm, 3.5 μm column  
1 Waters Symmetry C<sub>18</sub>, 3.9 x 150 mm, 5 μm column

Please include the MSDSs and the Certificates of Analysis for the samples and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Michael L. Trehy  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
06/26/2012



NDA 203505

**NDA ACKNOWLEDGMENT**

Shionogi Inc.  
Attention: Ting Chen, M.S.  
Director, Regulatory Affairs  
300 Campus Drive  
Florham Park, NJ 07932

Dear Ms. Chen:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ospemifene oral tablets 60mg

Date of Application: April 26, 2012

Date of Receipt: April 26, 2012

Our Reference Number: NDA 203505

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 25, 2012, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Project Manager, at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Margaret M. Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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MARGARET M KOBER  
05/23/2012  
Chief, Project Management Staff



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 67,216

**MEETING MINUTES**

QUATRx Pharmaceuticals Company  
Attention: Stuart Dombey, M.D.  
Chief Scientific Officer  
777 East Eisenhower Parkway, Suite 100  
Ann Arbor, MI 48108

Dear Dr. Dombey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ospemifene.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on September 29, 2009. The purpose of the meeting was to discuss your development plans for your NDA submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call George Lyght, R.Ph., at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Shelley R. Slaughter, M.D., Ph.D.  
Clinical Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 29, 2009, 1:00 PM  
**Meeting Location:** White Oak Building 22, Conference Room 1311

**Application Number:** IND 67,216  
**Product Name:** Ospemifene  
**Indication:** The treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause.  
**Sponsor/Applicant Name:** QUATRx Pharmaceuticals Company

**Meeting Chair:** Shelley R. Slaughter, M.D., Ph.D.  
**Meeting Recorder:** George Lyght, R.Ph.

### FDA ATTENDEES

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)  
Shelley R. Slaughter, M.D., Ph.D., Clinical Team Leader, DRUP  
Phill Price, M.D., Clinical Reviewer, DRUP  
Alexander Jordan, Ph.D., Pharmacologist, DRUP  
Sonia Castillo, Ph.D., Statistics Reviewer, Division of Biometrics III @ DRUP  
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA) @ DRUP  
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP) @ DRUP  
Chongwoo Yu, Ph.D., Clinical Pharmacology Reviewer, OCP @ DRUP  
Margaret M. Kober, R.Ph., M.P.A., Chief Project Management Staff, DRUP  
George Lyght, R.Ph., Sr. Regulatory Health Project Manager, DRUP

### SPONSOR ATTENDEES

Stuart Dombey, M.D., Chief Scientific and Regulatory Officer  
Robert Zerbe, M.D., Chief Executive Officer  
Christopher Nicholas, Chief Operating Officer  
Risto Lammintausta, Managing Director, Hormos Medical  
Mary Phelps, Senior Director, Clinical Development  
Rudolf Altevogt, M.D., Director, Regulatory Affairs  
Vivian Lin, M.D., Senior Director, Clinical Research

(b) (4)

(b) (4)

### BACKGROUND

QUATRx Pharmaceuticals Company (Sponsor) is developing ospemifene for the treatment of

moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. This meeting is to answer critical questions in preparation for the NDA submission. The IND was filed on March 25, 2003. Other meetings include a Guidance meeting on October 4, 2005, March 14, 2007 and on April 29, 2008.

## **DISCUSSION**

Preliminary responses to the meeting questions were provided to the sponsor on September 28, 2009. The discussion at the meeting is presented below in *bold italics*.

### **Questions:**

#### 1. Efficacy Data

- Based on the style of the supporting information in Tab 1, including the statistical analysis plan and draft shell report, is the ISE outline satisfactory?

***FDA Response:***

*Yes. The ISE outline is acceptable.*

- We plan to provide datasets for all Phase 3 studies (studies 15-50310, 15-50310X, 15-50312, 15-50718 and 15-50821). We will also provide integrated datasets for efficacy. Is this acceptable?

***FDA Response:***

*Yes. The dataset format is acceptable. We remind you that efficacy will be based on the results of each pivotal Phase 3 study (15-50310 and 15-50821), analyzed separately, and not on the overall ISE results.*

***Additional Clinical/Statistical Comments:***

*We request that you:*

- *Perform a weekly analysis of the change in baseline to Weeks 1,2,3,5,6,7,8,9,10 and 11 in the percentage of parabasal cells, percentage of superficial cells, vaginal pH and the most bothersome moderate to severe symptom of vaginal dryness and pain associated with sexual activity using the same analysis that you describe for the primary efficacy analysis at Week 12 and the secondary analysis at Week 4*
- *Perform a secondary analysis for the co-primary most bothersome moderate to severe symptom endpoints of vaginal dryness and pain associated with sexual activity using the ANCOVA model, as used for the primary efficacy analysis, that includes an indicator for vaginal lubricant use (Y/N) at week 12*
- *Perform the same analysis as requested in the second bullet for each week from Weeks 1 through 11*

*We remind you of our concern expressed on multiple occasions that your Phase 3 program may not have included the lowest effective dose. This is a review issue that is*

*likely to lead to a postmarketing commitment request as a condition of approval should the 60 mg dose prove to be safe and effective.*

**Meeting Discussion:**

*The Sponsor presented their preliminary efficacy data. Per the Sponsor, the 60 mg dose was statistically significantly superior to placebo in reduction of the symptoms of vaginal dryness and dyspareunia in the 310 Study, but statistical significance vs. placebo was achieved only for dyspareunia in the 821 Study. The Sponsor indicated that a higher than anticipated placebo effect explained the 821 results.*

*The Sponsor indicated that the studies did not collect data on the primary efficacy co-variables on a weekly basis. Only Weeks 4 and 12 data are available. Therefore, the requested secondary weekly analyses can not be provided.*

*The Sponsor indicated that they will be able to present a secondary ANCOVA with vaginal lubricant as an indicator at the Week 4 and 12 time points. The Sponsor will also provide a secondary analysis at Weeks 4 and 12 for all subjects who met the three baseline criteria of vaginal pH greater than 5, less than 5% superficial analysis on vaginal smear and at least one most bothersome moderate to severe vaginal symptom.*

**Post-Meeting Comments:**

**The Division would like to reiterate its previous recommendation that for this new molecular entity two confirmatory Phase 3 trials should be conducted.**

2. Clinical Safety Data

- Based on the style of the supporting information in Tab 2, including the statistical analysis plan and draft shell report, is the ISS outline and the selection of adverse events of particular interest satisfactory?

**FDA Response:**

*Yes. The ISS outline and the selection of adverse events of particular interest both appear to be satisfactory. We would also like the individual study report for each Phase 3 study to present the safety data separately for the respective study.*

- We plan to provide datasets for all Phase 3 studies (studies 15-50310, 15-50310X, 15-50312, 15-50718 and 15-50821). We will also provide integrated datasets for safety. Is this acceptable?

**FDA Response:**

*Yes.*

3. Based on centrally collected ECG data, which are presented in Tab 3, which demonstrate no QTc prolongation at 60mg ospemifene, we are seeking agreement to submit the results of the Thorough QTc study after the NDA submission. Is this acceptable?

***FDA Response:***

*No. We do not concur with submission of the Thorough QTc study after the NDA Submission. The NDA should be complete at the time of submission.*

***Meeting Discussion:***

***The Sponsor confirmed that the Thorough QTc study will be submitted at the time of NDA submission.***

4. Clinical pharmacology data will be summarized using commercially available eCTD templates from (b) (4). Based on the example of the drug drug interaction of the effect of ospemifene on warfarin pharmacokinetics presented in Tab 4 as both a written and tabular summary (parts of section 2.7.2 Summary of clinical pharmacology studies). Is the style of presentation of human pharmacokinetics acceptable?

***FDA Response:***

*In addition to the individual study summary, include the overall Clinical Pharmacology summary as well as Biopharmaceutics and Analytical Methods. Also, submit a table with all the clinical studies and formulations listed and a table summarizing the bioanalytical assay performance in each clinical study.*

***Meeting Discussion:***

***The Sponsor confirmed their plan to accommodate the Division's request.***

***Additional Clinical Pharmacology Comments:***

*We remind you that the following should be addressed:*

- *Dose proportionality and accumulation potential*
- *Drug interaction potential: Ospemifene appears to be an inhibitor of CYP 2B6 in vitro. As discussed at the Type C meeting held on April 29, 2008, you should examine the effects of ospemifene on substrates for CYP 2B6.*
- *Effect in patient with impaired renal function (as discussed at the Type C meeting held on April 29, 2008)*

***Meeting Discussion:***

***The Sponsor confirmed that they are planning to conduct a clinical study to examine the effects of ospemifene on substrates for CYP 2B6 and the results will be submitted at the time of NDA submission. However, they do not plan to conduct a renal impairment study and proposed that the absence of the renal impairment study be reflected in labeling. The Division requested that the Sponsor submit their justification(s) of not conducting a renal impairment study and indicated that the absence of this special populations study will be a review issue.***

**Post-Meeting Comments:**

**Renal impairment can adversely affect some pathways of hepatic/gut drug metabolism and has also been associated with other changes, such as changes in absorption, plasma protein binding, transport, and tissue distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug. The Agency is currently developing a guidance for industry to replace a previous guidance, “Pharmacokinetics in Patients With Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling” (renal guidance) issued in May 1998. It is recommended that renal impairment studies should be conducted for drugs that are metabolized and/or transported, in addition to drugs that are predominantly eliminated by the kidneys, to establish appropriate renal dose adjustment recommendations to facilitate optimal treatment in patients with kidney disease, which is a significant and growing segment of the US population. Reference is made to Zhang et al., Clin. Pharmacol. Ther. 85, 305-311 (2009) which reflects the Agency’s current thinking on this topic. Therefore, we recommend that you conduct a renal impairment study to evaluate the effect in patients with impaired renal function.**

5. Nonclinical Data

- Non-clinical data will be summarized using commercially available eCTD templates from [REDACTED] (b) (4). As examples sections of the pharmacology written summary (2.6.2), the pharmacology tabulated summary (2.6.3), the toxicology written summary (2.6.6) and the toxicology tabulated summary (2.6.7) are provided in Tabs 5 through 8. Is this way of presenting the data adequate?

***FDA Response:***

*Yes. However, a complete final report should be submitted for any nonclinical studies not previously submitted.*

- With regard to raw data sets from nonclinical studies we will provide the tumor datasets for the mouse and rat carcinogenicity studies. Is this acceptable?

***FDA Response:***

*Yes.*

- 6 Animal pharmacokinetics will be summarized in the pharmacokinetic written summary (2.6.4) and the pharmacokinetic tabulated summary (2.6.5). Examples are provided in Tabs 9 and 10. Is this way of presenting the data adequate?

***FDA Response:***

*Yes.*

7. CMC information

- **CMC information will be presented using the eCTD templates from (b) (4). Examples of the stability data presentation are provided in Tab 11. Is the presentation of the data adequate?**

***FDA Response:***

*Yes.*

- **Proposed starting materials for the synthesis of ospemifene are Starting Material (b) (4). (b) (4) The rational for the selection of these starting materials is provided in Tab 12. Do you agree?**

***FDA Response:***

The (b) (4) may be designated as the 'starting material' provided that:

- *A full information on the synthetic process for each 'starting material' is provided either in the NDA or in a DMF with the appropriate Letter of Authorization*
- *A commitment is made that the listed manufacturer(s) of each 'starting material' are the only manufacturers of the starting materials and that if there is any change in the manufacturing process at these sites or a new manufacturer is proposed after the NDA is approved, applicant will notify the FDA via a prior approval supplement*
- *Specifications of the 'starting materials' are established, and related substance in the 'starting material' are listed as "process impurities" in the drug substance specification, unless they are less than the detection limits*

***Meeting Discussion:***

*The Sponsor disagrees with the Division's recommendation for the second starting material, (b) (4). They believe it should be handled as a reagent. However, the Sponsor does agree that it may affect the structure of the final molecule.*

**Post-Meeting Comments:**

After further review, (b) (4) should still be designated as a starting material because it provides 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 will be less than that required for Starting Material I. Set specifications for the (b) (4) starting material and include the related substances in the drug substance specifications, as outlined in the third bullet point listed above. In addition, provide an overview in the NDA concerning

**the commercial availability of this starting material as part of the justification for why additional information is not necessary.**

8. **On January 7, 2009 we had requested advice on the design of our proposed bioequivalence study and the choice of the tablet batches that will be compared in this study. A copy of this request is attached in Tab13. Does the agency agree with the proposed design of the study and the choice of the tablet batches for the study?**

***FDA Response:***

*The choice of tablet batches is acceptable. However, the bioequivalence (BE) study bridging two formulations should be conducted as a single dose study under fasted conditions because this is generally considered to be the most sensitive in vivo setting to test similarity of immediate release (IR) formulations. Reference is made to Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations.*

*We recommend that you submit the full BE study protocol with appropriate scientific justification prior to conducting the study. When scientific justification provided in support of deviation from the guidance (i.e., fed BE study) is considered inadequate and when further confirmation is warranted to assure equivalent safety and efficacy of the two formulations in question, we may request additional BE data obtained under fasted conditions.*

*The BE study should be complete prior to the NDA submission and the data should be available in the NDA submission. Failure to provide information that establishes a link between the to-be-marketed formulation with the clinical trial formulations would be a significant review issue that could possibly result in our refusal to file the application.*

**Meeting Discussion:**

*The Sponsor shared their plan of conducting the BE study as a single-dose, replicate study under fasted conditions. The Division advised the Sponsor to submit a full protocol for review prior to initiating the study and the Sponsor agreed.*

9. Administrative issues

- We propose that all placebo-controlled Phase 3 studies be considered “covered” for financial disclosure. The specific studies are listed in Tab 14. Is the choice of the studies acceptable?

***FDA Response:***

No. Financial disclosure should be provided for all studies relied upon to determine either safety or effectiveness. In addition to the specific studies listed in your briefing package, this definition would include the bioequivalence study discussed in our response to Question 8.

- Many of our non-clinical and clinical research reports make reference to multiple publications which are not necessarily needed for the review of the application. We intend not to provide copies of all these references in the NDA submission but to make them available upon request. We will however include electronic copies of publications that are referenced in the summary documents because they will be needed to facilitate the review of the application. Is this acceptable?

***FDA Response:***

Yes.

10 Issues related to the electronic submission

- On May 28, 2009 we submitted our sample eCTD to the FDA. On June 17, 2009 we were informed by e-mail from CDER ESUB that our sample eCTD 900486 evaluation was successful. We have received a few minor general reminders and comments that we will take into account for the compilation of the eCTD submission. A copy of the June 17, 2009 e-mail from CDER ESUB is provided in Tab 15 for information. In line with the guidance, we will provide documents in PDF format with bookmarking from the Tables of Contents (TOCs), Lists of Tables, Lists of Figures, Lists of Appendices, etc. and hyperlinks from the body text to tables, figures, appendices, etc. if they are not on the same page. However, some very short “legacy” nonclinical reports in paper format do not have TOCs. For those reports we plan to provide scanned PDF files with bookmarks to all sections and hyperlinks if appropriate. This will allow quick navigation through the documents. We currently do not plan to add TOCs to these documents because this would disturb the page numbers (an example showing how the report and the added bookmarks will look on the computer screen is provided in Tab 16). Is this acceptable?

***FDA Response:***

Yes.

**Additional Meeting Discussion:**

**The Sponsor anticipates submission of their NDA in the second quarter of 2010.**

**ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Official meeting minutes to be conveyed in 30 days	FDA	October 29, 2009
A copy of the slides presented at the meeting will be sent to the FDA	Sponsor	October 30, 2009

**ATTACHMENTS AND HANDOUTS**

Slides Presented by QuatRx Pharmaceuticals Company.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-67216

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QUATRX  
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SHELLEY R SLAUGHTER  
10/29/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 67,216

QUATR<sub>x</sub> Pharmaceuticals Company  
Attention: Stuart L. Dombey, M.D.  
777 East Eisenhower Parkway  
Suite 100  
Ann Arbor, MI 48108

Dear Dr. Dombey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ospemifene.

We also refer to the meeting between representatives of your firm and the FDA on October 4, 2005. The purpose of the meeting was to discuss the requirements for an NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 796-2130.

Sincerely,

*{See appended electronic signature page}*

Shelley R. Slaughter, M.D., Ph.D.  
Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** October 4, 2005  
**TIME:** 11:30 – 1:00 p.m.  
**LOCATION:** White Oak; Conf. Rm 1313  
**APPLICATION:** IND 67,216  
**DRUG NAME:** Ospemifene  
**TYPE OF MEETING:** End of Phase 2

**MEETING CHAIR:** Shelley R. Slaughter, M.D., Ph.D., Team Leader, Division of Reproductive and Urologic Products (DRUP), HFD-580

**MEETING RECORDER:** Kassandra Sherrod, R.Ph., Regulatory Project Manager, DRUP HFD-580

**FDA ATTENDEES:**

Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation (ODE) III, HFD-103  
Shelley R. Slaughter, M.D., Ph.D., Team Leader, DRUP, HFD-580  
Phill Price, M.D., Medical Officer, DRUP, HFD-580  
Wafa Harrouk, Ph.D., Pharmacologist, DRUP, HFD-580  
Lynnda Reid, Ph.D., Pharmacology Team Leader, DRUP, HFD-580  
Ameeta Parekh, Ph.D., Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUP, HFD-580 (via telephone)  
Moh-Jee Ng, M.S., Statistician, Division of Biometrics II, DBII, HFD-715  
Kassandra Sherrod, R.Ph., Regulatory Project Manager, DRUP, HFD-580

**EXTERNAL CONSTITUENT ATTENDEES:**

Stuart Dombey, M.D., Chief Scientific and Regulatory Officer, QuatRx Pharmaceuticals  
Randall Whitcomb, M.D., Chief Medical Officer, QuatRx Pharmaceuticals  
Constance Keyserling, Head of Development Operations, QuatRx Pharmaceuticals  
Patrice Mason, Development Scientist, QuatRx Pharmaceuticals  
Risto Lammintausta, M.D., Ph.D., Managing Director, Hormos Medical  
Janne Komi, M.D., V.P., Clinical Research, Hormos Medical  
Kaija Halonen, Project Director, Hormos Medical

(b) (4)

**BACKGROUND:**

Ospemifene is a selective estrogen receptor modulator (SERM) being developed by Hormos Medical for the treatment of vulvar and vaginal atrophy. A pre IND meeting was held on July 1, 2002, to discuss Phase 3 clinical trials. The IND was filed on March 25, 2003.

**MEETING OBJECTIVES:**

To discuss the requirements for an NDA.

**DISCUSSION POINTS:**

**QUESTION #1:** *We are submitting a tabular summary of the completed toxicology studies with this pre-meeting briefing document and will want advice as to whether or not this battery of studies is adequate for approval*

**Division Response:** No. A multi-generational reproductive and developmental study in at least one species is required at the time of the NDA submission. Please refer to *ICH-S5A Detection of Toxicity for Reproduction for Medicinal Products* for further details.

Additional nonclinical points discussed at the meeting:

- Chronic toxicology studies may be conducted with only the relevant sex, however, when only one sex is used, the number of animals/group should be significantly higher. We generally recommend doubling the number.
- Data were presented demonstrating that lipid vehicles may increase systemic exposures. Please submit repeat dose range-finding studies to support either your choice of vehicle for new studies or to demonstrate that the use of a lipid based vehicle will not significantly enhance absorption and therefore the studies conducted to date constitute maximum feasible dosing. In the event that neither 0.5% CMC nor corn oil are considered good vehicles for maximum drug exposure, you may consider conducting dietary admixture studies especially in light of the clinical increase in drug exposure with food.
- It was agreed that DRUP would review the proposed 28-day monkey study and determine at that time if the chronic toxicology study in monkeys would need to be repeated to achieve higher systemic exposure multiples of the human dose.

**QUESTION #2:** *Two-year carcinogenicity studies are planned for mouse and rat following a 12-week dose-finding study in the mouse. We propose to present the protocols to the Carcinogenicity Advisory Committee after the mouse study data is available and prior to commencing carcinogenicity studies. Is this acceptable?*

**Division Response:** Yes. The Sponsor should refer to guidance documents *ICH-S1B Testing for Carcinogenicity of Pharmaceuticals, ICH-S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals, and Carcinogenicity Study Protocol Submissions and the Guidance for Industry, Statistical Aspects of the Design, Analysis, and Interpretation of chronic Rodent Carcinogenicity Studies of Pharmaceuticals*". Please note that when designing Carcinogenicity studies protocols to include both sexes need to be evaluated regardless of the indication sought for the drug product.

**QUESTION #3:** *Full draft protocols for the proposed Phase 1/11 studies are included in this pre-meeting briefing document. Are the proposed study designs and sample sizes adequate for approval for this indication?*

**Division Response:** The number of subjects to totally assess the primary endpoints may not be adequate. For assessment of VVA associated with the menopause, the Agency recommended 3 co-primary endpoints:

- a. Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome.
- b. Mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants would have a vaginal pH > 5.0. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- c. Mean change from baseline to week 12 in vaginal maturation index (proportions of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5% superficial cells on a vaginal smear. The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.

**QUESTION #4:** *The total number of subjects needed for adequate short and long term treatment exposure is not addressed in the Guidance for Industry for this indication. Therefore, we are relying on the ICH-E1A guideline (The extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term treatment and Non-Life Threatening Conditions) which states that approximately 1500 subjects should be exposed short-term and 100 subjects should be exposed for a least one year. Does the Agency concur that this is sufficient?*

**Division Response:** No; this is a NME. Approximately 380 subjects will receive the 60mg dosage. Of this total, up to 50% of subjects may not have a uterus. This reduces to 190, the total number of subjects available to assess endometrial safety. This assumption for available numbers does not take into consideration further reduction in the number of available subjects because of drop-outs. You should consider both of these influences when considering the total number of subjects to study. At a minimum, we recommend that you have approximately 100-200 subjects with a uterus per dosage arm to assess endometrial safety.

QUATR<sub>x</sub> response:

We will consider your recommendations in assessing the total numbers for subjects exposure.

**QUESTION #5:** *We proposed to limit the maximum dose to 60 mg for the indication of treatment of moderate to severe vulvar and vaginal atrophy in postmenopausal women. We expect this will be an effective dose. We also intend to study the 30 mg as a minimally effective dose and the studies will be placebo controlled. Does the Agency require any other dose levels to be studied?*

**Division Response:** During our telecon with the sponsor on June 10, 2003 we recommended an intermediate dose of 45 mg in order to define the lowest effective dose (LED). This recommendation was made under the assumption that the 45 mg dose may be the LED, while the 30 mg dose may be an ineffective dose. Therefore, you should consider treatment arms of 30mg, 45mg and 60mg.

QUATR<sub>x</sub> response:

We will discuss the dosages to be studied again. We view the 30 mg dose as potentially borderline for efficacy. It may or may not meet the criteria for efficacy as delineated in the 2003 Draft Guidance. We do not plan on conducting the two “proof of efficacy” trials concurrently. We may use the information gained in the first study to plan our doses for study in the next trial. If the 30 mg dose appears to be efficacious we will study a lower dose in the second trial.

**Division Response:** In addition, we would recommend that the placebo be composed of a vaginal lubricant. Therefore, this study should be double-blinded double-dummied.

**QUESTION #6** Hormos is proposing long-term studies to obtain 6- and 12-months data on the 30 and 60-mg doses, including endometrial changes. The Guidance for estrogen/progestin drugs for this indication states that the background incidence rate for endometrial hyperplasia is 0%-1%. Is the recommended target hyperplasia rate of less than or equal to 1% with an upper bound on the one-sided 95% confidence interval that does not exceed 4% also appropriate for a product of this class (SERM)?

**Division Response:** Yes. It is the Division’s recommendation that the recommendations in the 2003 Draft Guidance for assessing the risk of endometrial hyperplasia should be followed for this SERM drug product.

**QUESTION #7:** Are the attached plans for approaching endometrial biopsies acceptable?

**Division Response** No

Per the 2003 Draft Guidance Document, we recommend that, **as a safety assessment,** all subjects who have a uterus undergo an endometrial biopsy **at baseline and at week 12.** If after a valid attempt has been made to sample the endometrium, the **week 12** endometrial biopsy results confirm insufficient endometrial tissue for diagnosis, a transvaginal ultrasound (TVU) result of a double-wall endometrial thickness of < 4mm could be considered as not indicative of endometrial hyperplasia.

In addition, to support internal consistency in your study, it is strongly recommended that all TVUs be read at a central laboratory. TVUs should be done at baseline, 6 and 12 months.

It is recommended that all subjects with a TVU demonstrating an endometrial stripe of greater than or equal to 4mm (not  $\geq$  5mm) be biopsied.

In addition, for the extension study a biopsy should be obtained at the end of the study. (Visit 6—12 months).

A TVU and endometrial biopsy should be performed at 12 months (Visit 6)

**QUESTION #8** We are proposing to include up to 50% of post-hysterectomy patients in the Phase 3 trials, is this acceptable?

**Division Response:** YES; however, with 50% of subjects not having a uterus, the sample size may be too small to support long-term safety of this product. (Refer to question #4).

**QUESTION #9:** Are thorough QTc studies required for selective estrogen receptor modulators? If not, will one baseline and one post date dose ECG during the Phase III studies be sufficient?

**Division Response:** Since this a NME, we recommend that you conduct a thorough QTc study. . Please consult ICH Technical Requirements for Registration of Pharmaceuticals for Human Use. The document is entitled “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for non-Antiarrhythmic Drugs E14; Dated May 12, 2005.

**QUESTION #10:** We are submitting a lot of proposed human drug interactions studies in this pre-meeting briefing document and would like you advice as to whether or not this set of studies is adequate for approval.

**Division Response:**

The induction potential of ospemifene should be evaluated by conducting in-vitro studies. In-vivo induction-based interaction studies may be necessary depending on the results of in-vitro studies.

(b) (4)

The sponsor stated that the formation of 4-hydroxyospemifene seems to be catalyzed by CYP2C9 and CYP2C19, and to less extent by CYP2B6 and CYP3A4. In addition, ospemifene is a modest competitive inhibitor of CYP2B6 and CYP2C9 and less potent inhibitor of CYP2C19 and CYP2D6. The principal metabolite, 4-hydroxyospemifene seems to be a more potent inhibitor of the same enzymes than its parent compound. Effects of ospemifene on CYP2B6 and CYP2D6 substrates should be addressed. Effects of CYP2C9, CYP2C19 and CYP2B6 inhibitors on ospemifene metabolism should be addressed.

The metabolic pathway of 4-hydroxyospemifene should be addressed.

**Additional Division statistics comments:**

Please define improvement/desirable response for the four co-primary efficacy variables: most bothersome VVA symptom, two maturation indices, and vaginal pH.

**Please be advised that there is a risk that your calculated sample size may not be adequate to demonstrate efficacy due to the following reasons:**

- Use of estimates for most bothersome symptom response rates from another product.
- Use of estimate for only one dose of ospemifene, 30 mg, for maturation indices 1 and 3 of vaginal smear.
- Use of estimates for mean decrease in vaginal pH from the literature and not based on ospemifene.

**Please submit all case report forms and relevant investigator/lab brochures for review.**

**ACTION ITEMS:**

Meeting minutes will be sent to sponsor within 30 days.

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Kassandra C. Sherrod  
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