

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-252, Original 1

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # NDA 022252

SUPPL #

HFD # 580

Trade Name Natazia

Generic Name estradiol valerate tablets and estradiol valerate/dienogest tablets, 3mg,1mg and 2mg/2mg, 2mg/3mg

Applicant Name Bayer HealthCare Pharmaceuticals, Inc.

Approval Date, If Known May 6, 2010

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# 009402

Delestrogen (estradiol valerate)

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:

Study 306660 (Europe) and Study 304742 (US/Canada)

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"):

Study 306660 (Europe) and Study 304742 (US/Canada)

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 # YES ! NO
! Explain:
Study conducted in Europe, IND not required

Investigation #2 !
IND # 064809 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:
The applicant provided support for
the study

(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: Pam Lucarelli
Title: Regulatory Health Project Manager
Date: May 6, 2010

Name of Office/Division Director signing form: Julie Beitz
Title: Office Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	Natazia

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

/s/

JENNIFER L MERCIER
05/06/2010

JULIE G BEITZ
05/06/2010

PEDIATRIC PAGE**(Complete for all filed original applications and efficacy supplements)**NDA/BLA#: NDA 022252Supplement Number: N/ANDA Supplement Type (e.g. SE5): N/ADivision Name: Division of
Reproductive and Urologic Drug
Products (HFD-580)PDUFA Goal Date: 5/6/2010Stamp Date: 7/6/2009Proprietary Name: (b) (4)Established/Generic Name: estradiol valerate/dienogestDosage Form: tabletsApplicant/Sponsor: Bayer HealthCare Pharmaceuticals, Inc.Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____
-

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): 2(Attach a completed Pediatric Page for each indication in current application.)**Indication:** Primary Indication: Prevention of pregnancy**Q1:** Is this application in response to a PREA PMR? Yes ContinueNo 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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. <u>0</u> mo.	<u>12</u> yr. <u>0</u> mo.	<input checked="" 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) 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 †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<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).

Additional 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

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 checked="" type="checkbox"/>	Other	<u>12</u> yr. <u>0</u> mo.	<u>16</u> yr. <u>11</u> mo.	<input checked="" 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 Health Project Manager

(Revised: 6/2008)

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

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Secondary Indication: Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q2: 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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	12 yr. 0 mo.	<input checked="" 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 Section 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) 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 some or all 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 pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

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 checked="" type="checkbox"/>	Other	12 yr. 0 mo.	16 yr. 11 mo.	<input checked="" 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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Health Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)



Bayer HealthCare Pharmaceuticals Inc, hereby certifies that it did not and will not use in any capacity any persons (employees, contractors/subcontractors, or consultants) debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with New Drug Application 22-252.

Further, Bayer HealthCare Pharmaceuticals Inc. certifies that all clinical investigators participating in the five (5) clinical studies² that are pivotal in the support of the efficacy and safety of EV/DNG Tablets for the indications sought¹ have not been debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act. A full listing of the Principal Investigators for each clinical study is provided in the attached.

John Talian, PhD



Vice-President, US Regulatory Affairs
Bayer HealthCare Pharmaceuticals

¹ Primary Indication: For the prevention of pregnancy in women who elect to use an oral contraceptive.

Secondary Indication: For the treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose oral contraception.

² Five clinical studies have been included: three studies for which we are also providing financial disclosure as agreed with the Division at our 17 Dec 2007 Pre-NDA meeting for the oral contraception indication. In addition, debarment and financial disclosure information are provided for the two pivotal studies supporting the heavy menstrual bleeding indication.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-252 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Natazia Established/Proper Name: estradiol valerate (EV) estradiol valerate/dinogest (DNG) Dosage Form: 3.0 mg EV, 2.0 mg EV + 2.0 mg DNG, 2.0 mg EV + 3.0 mg DNG and 1.0 mg EV tablets		Applicant: Bayer HealthCare Pharmaceuticals Agent for Applicant (if applicable):
RPM: Pamela Lucarelli		Division: Division of Reproductive and Urologic Products (DRUP)
<p>NDA: 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(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"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		May 6, 2010
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR For Prevention of Pregnancy Only
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None

¹ 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.

<p>❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</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 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <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</p> <p>Comments: _____</p>	
<p>❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____</p>	<p>March 3, 2010</p>
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes, date
<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"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<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

² All questions in all sections pertain 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<input checked="" 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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	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"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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> 	<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
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ 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
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approved – May 6, 2010 (Prevention of pregnancy indication only)
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	Included
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Included EMEA Labeling
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/26/09

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	Included
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	Included
❖ Proprietary Name <ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	Qlaira – December 22, 2009 (b) (4) Natazia – May 5, 2010
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP May 5, 2010 <input checked="" type="checkbox"/> DRISK March 23, 2010 <input checked="" type="checkbox"/> DDMAC April 1, 2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	Included – August 24, 2009
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ 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 (except previous action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date of mtg; approvals only</i>) 	<input type="checkbox"/> Not applicable March 3, 2010
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>) 	<input type="checkbox"/> Not applicable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg December 18, 2007 and February 5, 2009
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 6, 2010
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 6, 2010
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 6, 2010
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None May 4, 2010
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See CDTL Review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	April 30, 2010
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	Included
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Included
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None QT Review
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo (<i>indicate date</i>) 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
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 5 Sites Included
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/26/09

Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 15, 2010
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None April 2 and May 6, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None May 4, 2010
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None January 27, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	X None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None May 6, 2010
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 17, 2009, March 23 and May 6, 2010
• ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	March 23, 2010
<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	

<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	<p>Date completed: May 6, 2010</p> <p><input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation</p>
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation</p> <p>Date completed:</p> <p><input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold</p>
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<p><input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed</p>

Appendix A 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	Natazia

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/s/

JENNIFER L MERCIER
05/06/2010

MEMORANDUM

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

DATE: April 27, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Lucarelli, Pamela K
Sent: Tuesday, April 27, 2010 1:08 PM
To: 'Mark Rosengarten'
Subject: RE: NDA 22-252 - Response to Clin Info Request Dated 31 Mar 2010 Seq 0019

Mark,

Please respond as soon as possible.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

From: Mark Rosengarten [mailto:mark.rosengarten@bayer.com]
Sent: Tuesday, April 27, 2010 10:54 AM
To: Lucarelli, Pamela K
Subject: RE: NDA 22-252 - Response to Clin Info Request Dated 31 Mar 2010 Seq 0019

Hi Pam,
I am in receipt of this email.
Best Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>

cc

Subject RE: NDA 22-252 - Response to Clin Info Request Dated 31 Mar 2010
Seq 0019

04/27/2010 08:41 AM

4/27/2010

Hi Mark,

Below is a clarification request of the data submitted on April 6, 2010 (see correspondence below):

1. Clarify/correct the maximum number of bleeding days reported on Table 2, Cycles 2 (75 days), 10, 11, 18 and 19 in Study 306660 and on Table 2 for Study 304742 (Cycle 1). Maximum number of days also appears inaccurate in Table 2 for Study 304004.
2. If review of these data indicates that the entire submission may be unreliable, recalculate and send the corrected tables as soon as possible.
3. Clarify/correct the sample size reported on Table 3 and Table 4. Clarify also why the sample size for unscheduled (intracyclic) bleeding/spotting is so much lower than that for scheduled bleeding/spotting in all 3 trials. Were subjects included in the descriptive data only if they reported affirmatively that they had experienced unscheduled bleeding/spotting? [this was changed from previously]
4. Provide the number and percent of subjects who experienced amenorrhea (no scheduled or unscheduled bleeding or spotting) by cycle in each trial.

If you have any questions, please let me know. Confirm receipt of this email.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

From: Mark Rosengarten [mailto:mark.rosengarten@bayer.com]
Sent: Tuesday, April 06, 2010 6:24 PM
To: Lucarelli, Pamela K
Subject: NDA 22-252 - Response to Clin Info Request Dated 31 Mar 2010 Seq 0019

Hi Pam,
Attached for your information is Bayer's response to the Clinical Information Requested on 31 March 2010 for NDA 22-252. This will be submitted to the gateway ASAP.

4/27/2010

Please acknowledge receipt of this email and let me know if you have any additional questions.

Best Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

Qlaira

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/s/

PAMELA LUCARELLI
04/27/2010

MEMORANDUM

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

DATE: April 22, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Lucarelli, Pamela K
Sent: Friday, April 23, 2010 10:11 AM
To: 'Mark Rosengarten'
Subject: RE: NDA 022252 Clinical Information Request

Hi Mark,

Yes, Ss = Subjects.

Please let me know if you need anything else.

Pam

From: Mark Rosengarten [mailto:mark.rosengarten@bayer.com]
Sent: Thursday, April 22, 2010 4:00 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Clinical Information Request

Hi Pam,
I received your email but I have a question, just need to be sure I understand a term. Did any Ss (if so, how many Ss, by arm and by study) have 0 MBL imputed in the absence of any data on bleeding intensity and collection of sanitary products? What is Ss -- does this mean Subjects?

Thanks Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>

cc

Subject NDA 022252 Clinical Information Request

04/22/2010 02:41 PM

Hi Mark,

Per our phone conversation, below is the clinical information request.

There were a large number of protocol violations in Studies 308960 and 308961. You note that 2 major reasons for violations were

4/23/2010

- bleeding intensity data missing for 2 or more consecutive days
- bleeding intensity data missing for > 10% of days

1. Provide the number of subjects in each arm by study who had each type of violation
2. Clarify the imputation of MBL data for Type 3 missing data scenario. Did any Ss (if so, how many Ss, by arm and by study) have 0 MBL imputed in the absence of any data on bleeding intensity and collection of sanitary products?
3. Clarify the e-diary failure that occurred in Study 308961. Provide information on the number of Ss impacted by this, whether original data was lost during the failure, how lost data were handled, and extent to which a paper diary was used. Describe whether some Ss only used the paper diary, or whether the paper diary was an intermittent substitution during a period when the e-diary was not functioning. Provide information on the number of cycles and number of Ss who used the paper diary.

Please confirm receipt of this email, and respond by close of business April 23, 2010.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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PAMELA LUCARELLI
04/23/2010

MEMORANDUM

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

DATE: April 20, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Post Marketing Requirements

APPLICATION/DRUG: NDA 022252

The correspondence below is notification of post marketing requirements.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Tuesday, April 20, 2010 10:12 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 PMR
Attachments: CLINICAL PMR request.doc

Hi Pam,
I have received this email, Pam have you heard anything (or received any feedback) regarding the review of the HMB proposal we sent you?

Best Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e.mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 PMR

04/20/2010 08:27 AM

Hi Mark,

Attached is the post marketing requirement. Within the document there is a comment which we need you to address. Please have the suggested dates to us by COB on April 21, 2010. If you have any questions, let me know.

Confirm receipt of this email.

Thanks,
Pam

<<CLINICAL PMR request.doc>>

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue

4/20/2010

Silver Spring, MD 20903

Phone 301.796.3961

Fax 301.796.9897

pamela.lucarelli@fda.hhs.gov

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PAMELA LUCARELLI
04/20/2010

MEMORANDUM

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

DATE: April 15, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is a CMC information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Thursday, April 15, 2010 11:19 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Established Name

Received!

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>, "MaryRose
Salvacion" <maryrose.salvacion@bayer.com>, "Suzanne Hampton"
<suzanne.hampton@bayer.com>

04/15/2010 11:14 AM

cc
Subject NDA 022252 Established Name

Hi Mark,

Below is the established name. Please confirm receipt of this email.

**Tradename (estradiol valerate tablets and estradiol valerate/dienogest tablets) 3mg,1 mg and 2mg/2mg,
2mg/3mg**

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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4/16/2010

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Thursday, April 15, 2010 11:20 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Labeling

Received!

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 Labeling

04/13/2010 07:49 AM

Hi Mark,

We recommend that you make the following changes to your packaging:

- The established name for the drug product is under review due to the unique combination of the drug substance (more than one combination of drug substances) within one blister card.
- The dosage strengths are not included in the primary panel of both immediate container (blister) and carton labels.
- Lot number and expiration date block is not assigned on carton label.
- Please increase the font size of the established name on carton label to more than 50% of the trade name.
- "See enclosed information" on the carton label should be reworded as "See package insert for dosage information".

Please acknowledge receipt of this email. Let me know if you have any questions.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager

4/16/2010

FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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/s/

PAMELA LUCARELLI
04/16/2010

MEMORANDUM

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

DATE: April 6, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Wednesday, March 31, 2010 9:38 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 22252 Information Request

Dear Pam,
 Just received it today Wednesday 3/31/10 as I was out for the Passover Holiday. I will call you to make sure you have received the email and gateway response to the QT/Qc questions.
 Best Regards Mark

Mark Rosengarten
 Global Regulatory Affairs
 Bayer HealthCare Pharmaceuticals, Inc.
 Phone: 973-487-2784 / Fax: 973-487-2016
 e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
 <Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
 cc
 Subject NDA 22252 Information Request

03/29/2010 02:19 PM

Hi Mark,

Please see the clinical information request below:

Provide tables based on 28-day cycles for the analysis of:

- Scheduled bleeding days
- Scheduled spotting days
- Unscheduled bleeding days
- Unscheduled spotting days

In the following studies:

- Study 306660 (Report A35179)
- Study 304742 (Report A39818)
- Study 304004 (Report A 35644)

Use the following columns to display that data. Submit data for all cycles studied.

Cycle	N	Mean (SD)	Minimum	Median	Maximum
		1			
		2			

4/6/2010

3
4
Etc.

Please provide the data by COB on April 6, 2010. Acknowledge receipt of this email.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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Application
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Submission
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Submitter Name

Product Name

NDA-22252

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

Qlaira

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

/s/

PAMELA LUCARELLI
04/06/2010

MEMORANDUM

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

DATE: March 25, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: QT Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is a QT information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Wednesday, March 24, 2010 2:52 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Information Request

Hi Pam,
Your request has been received!
Thank You, Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e.mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 Information Request

03/24/2010 10:50 AM

Hi Mark,

Please review the information request (regarding the QT studies) below and provide a response by Friday, March 26, 2010.

The largest QTcF change associated with 400 mg moxifloxacin appears to be much higher than typically observed. We would like to understand if this is caused by moxifloxacin concentration for the study population. Please submit the corresponding plasma concentration data for moxifloxacin.

Acknowledge receipt of this email. If you have any other questions, please let me know.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961

3/25/2010

Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

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/s/

PAMELA LUCARELLI
03/25/2010

MEMORANDUM

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

DATE: March 10, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Wednesday, March 10, 2010 12:22 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Information Request

Dear Pam,
Thank you, we have received your request.
Best Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e.mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 Information Request

03/10/2010 10:36 AM

Hi Mark,

Please provide the following information in regard to EV/DNG (final regimen) exposure in your clinical trials:

- Number of completed 28 day cycles
- Number of partially completed 28 day cycles
- Total days exposure to EV/DNG in safety analysis set (Include placebo days and days from partially completed cycles)
- Total women-years exposure to EV/DNG in safety analysis set (Include placebo days and days from partially completed cycles)

Also provide this information individually for each of the following studies (protocol numbers):

A39818 (304742)
A35179 (306660)
A35644 (304004)
A33022 (301886)
A38220 (310122)
A25364 (307300)

A29849 (308960)

3/10/2010

A42568 (308961)

Provide this information by close of business March 18, 2010. Acknowledge receipt of this email as soon as possible. If you have any questions, please let me know.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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3/10/2010

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NDA-22252

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/s/

PAMELA LUCARELLI
03/10/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Office of Surveillance and Epidemiology (OSE)
Attention: Maria Wasilik 301-796-0567

FROM (Name, Office/Division, and Phone Number of Requestor): Division of Reproductive and Urologic Drug Products (HFD-580)
Pamela Lucarelli 301-796-3961

DATE
March 4, 2010

IND NO.

NDA NO.
022252

TYPE OF DOCUMENT
Original

DATE OF DOCUMENT
July 6, 2009

NAME OF DRUG
(b) (4) (Estradiol
Valerate/Dienogest)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
March 29, 2010

NAME OF FIRM: Bayer HealthCare Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the patient instructions (labeling), specifically the missed tablets section. Attached are the instructions used in the clinical trial regarding missed tablets. There are several differences between the labeled instructions and those used in the trials. Instructions in labeling must be consistent with those used in the demonstration of safety and efficacy. The applicable label is available through EDR. The PDUFA goal date is May 6, 2010. Please review and make recommendations by the above due date.

SIGNATURE OF REQUESTOR
Pamela Lucarelli (delivered through DARRTS)

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Missed tablet rules

In case of missed tablets, the volunteer is to take the missed tablet as soon as she remembers. If she is **less than 12 hours** late in taking one of the hormone tablets, contraceptive protection is not reduced. No further action is needed.

Days	Content of EV / DNG	Delay of <u>more than 12 hours</u>
1 – 2	3.0 mg EV	1. take missed tablet immediately and the following tablet as usual, 2. use of back-up contraception until <u>day 9</u>
3 - 7	2.0 mg EV + 2.0 mg DNG	1. take missed tablet immediately and the following tablet as usual, 2. back-up contraception for the next <u>7 days</u>
8 – 17	2.0 mg EV + 3.0 mg DNG	
18 – 24	2.0 mg EV + 3.0 mg DNG	1. take missed tablet and <i>continue tablet intake as usual (use up the blister in the given sequence)</i> 2. use of back-up contraception until <u>day 9</u> of the following cycle
25 – 26	1.0 mg EV	intake of missed tablet (no further action)
27 – 28	placebo	

Not more than two tablets are to be taken on a given day.

In case of vomiting within 4 hours after tablet intake, absorption may not be complete. In such an event, another tablet with the same color has to be taken from the reserve blister. The same procedure applies for diarrhea.

A menstruation-like withdrawal bleeding is supposed to occur usually after day 24 of a treatment cycle (light yellow tablets, last tablet of a cycle containing both hormones). If such bleeding fails to occur, pregnancy is to be ruled out by performing a HCG test immediately before starting the next EV / DNG combination (day 3 of the subsequent cycle: medium red tablet).

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/s/

PAMELA LUCARELLI
03/04/2010

3 pp. withheld in full immed. after this page as (b)(4) CCI/TS.

MEMORANDUM

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

DATE: January 5, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Information Request

APPLICATION/DRUG: NDA 022252

The correspondence below is an information request for more data to be submitted to the ECG Warehouse.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Tuesday, January 05, 2010 12:03 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Request

Hi Pam,
Its hard to believe it is 2010. Happy New year to you as well. I am confirming that I have received the email request below and we have started the wheels in motion to respond.
Best Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 Request

01/05/2010 10:57 AM

Hi Mark,

Happy New Year! According to our data manager there is data missing from the dataset submitted to the ECG warehouse. Please submit the following items as soon as possible.

1. ECG dataset in raw duplicates with QTCB, QTCF, QTCL, QTCL correction factor (slope) and actual ECG date/time (up to second) information added.
2. PK dataset with plasma concentrations at nominal time points.

If you have any questions please let me know. In addition, please confirm receipt of this email.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961

1/5/2010

Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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Product Name

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/s/

PAMELA LUCARELLI
01/05/2010

MEMORANDUM

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

DATE: December 17, 2009

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Information Request

APPLICATION/DRUG: NDA 22-252, Qlaira

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Thursday, December 17, 2009 5:12 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Information Request

Hi Pam,
I have received this request.
Best Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e.mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 Information Request

12/17/2009 10:56 AM

Hi Mark,

Below is in an information request. Please acknowledge receipt of this email.

Thanks,
Pam

In regard to contraceptive efficacy your label indicates the following information:

(b) (4)

You have expressed exposure time in days without backup contraception. The Division's practice is to exclude from calculation of the Pearl Index all 28-day cycles in which backup contraction (including condoms) was used. Provide the number of 28-day treatment cycles with no use of backup contraception in Studies 306660, 304742 and 304004 (individually and total)?

12/28/2009

If the reported Pearl Indices were based on exclusion of single days in which backup contraction was used, provide a recalculation based on the Division's algorithm.

Subject 519008 in study 304742 was last seen at Visit 9 (Sept 13, 2006). Diary information records her last study drug use in August, 2006 but it was later reported that she last took study drug on Jan 23, 2007.

How many study tablets did she have at home after (Visit 9 date) – i.e., was she provide with an additional pill supply at that time? If so, how many cycles of pills was she given? Did she return empty pill packs at Visit 9? Did they corroborate her report at that time of when she last took study drug?

Is there any additional information on this subject who was lost to follow up?

"Subjects 520005, 520015 and 608006 have vasectomized partners. The corresponding cycles after their partners were vasectomized should be excluded in the calculation of Pearl Index.

Please update the Pearl Index by excluding those cycles.

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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/s/

PAMELA LUCARELLI
12/28/2009

REQUEST FOR CONSULTATION

TO (Office/Division)
Division of Cardiovascular and Renal Products
QT interdisciplinary Review Team
Devi Kozeli, RAC
Assistant to the Division Director

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Reproductive and Urologic Products
Pamela Lucarelli
Regulatory Health Project Manager
301-796-3961

DATE
December 15, 2009

IND NO.

NDA NO.
022252

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
July 6, 2009

NAME OF DRUG
Qlaira (estradiol
valerate/dienogest tablets)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
February 19, 2010

NAME OF FIRM: Bayer HealthCare Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

We are requesting your review of the QT study for NDA 022252 (Fully electronic and can be viewed through EDR). This NDA is designated a standard review and the PDUFA Goal Date is May 6, 2010.

SIGNATURE OF REQUESTOR
Pamela Lucarelli

METHOD OF DELIVERY (Check one)
 DARRTS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

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/s/

PAMELA LUCARELLI
12/15/2009

MEMORANDUM

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

DATE: November 12, 2009

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 22-252, Qlaira

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Tuesday, November 10, 2009 2:07 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Clinical Information Request

Hi Pam,
We are now working on providing the information requested. I will be in touch.
Thank you!
Best Regards, Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>
cc
Subject NDA 022252 Clinical Information Request

11/10/2009 11:27 AM

Hi Mark,

The following is a clinical information request:

1. For the contraceptive studies 306660 (Report A35179) and 304004 (Report A35644) incorporate into all the previously submitted clinical datasets information on the name and identification number of all the principal investigators and the country for all rows in the datasets.
2. For the contraceptive studies -- 306660 (Report A35179), 304004 (Report A35644) and 304742 (Report A39818) and the DUB studies -- 308960 (Report A29849) and 30891 (Report A42568) provide a detailed analysis of the impact of concomitant medications that may have a beneficial effect on test product efficacy (e.g., additional hormones in the contraceptive trials; hormones or tranexamic acid in the DUB trials)

Provide tabular and data set listings that include the following columns:

Volunteer identification number
Investigator name
Site number
Country
Concomitant medication name (the ones with potential efficacy)
Class of drug
Cycle(s) during which the concomitant medication was used

11/12/2009

Number of days concomitant medication was used
Description of the adjustments made to the efficacy analysis

If you have any questions about the request, please let me know. In addition, please confirm receipt of this request (via e-mail).

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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PHARMACEUTICA
LS INC

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/s/

PAMELA LUCARELLI
11/12/2009

MEMORANDUM

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

DATE: October 29, 2009

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: **Statistical Information Request**

APPLICATION/DRUG: NDA 22-252, Qlaira

The correspondence below is a statistical information request.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Thursday, October 29, 2009 9:47 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 22-252 Information Request
Importance: High

Hi Pam,

I am sending you this email to acknowledge receipt of the statistical request received from you (see below) and to let you know we are working on providing you with the information requested. I also want to verify for you that I left you a voice message acknowledging receipt of the this email on the day I received it (10/26/09) and left you a message this morning as well. Please let me know if you have any additional questions at this time.

Thank you.

Best Regards, Mark

Mark Rosengarten
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.
Phone: 973-487-2784 / Fax: 973-487-2016
e:mail: mark.rosengarten@bayer.com

"Lucarelli, Pamela K"
<Pamela.Lucarelli@fda.hhs.gov>

To "Mark Rosengarten" <mark.rosengarten@bayer.com>

cc

Subject NDA 22-252 Information Request

10/26/2009 10:51 AM

Hi Mark,

Below are three statistical requests. Review and respond as soon as possible.

Thanks,
Pam

In addition, please confirm receipt of this email.

1. We can not reproduce the analysis datasets based on your datasets and programs. We first ran the program "fda-data-sets-eff-oc.sas". This program calls datasets randoo, asaov, and pd, which were missing in your submission. Please provide datasets RANDO, ASAOV and PD for the ISE analysis.

2. There is no variable to identify country in Study 306660 (A35179). Please provide country information per subject id.

10/29/2009

3. Please clarify why you made the corrections on the following case.
- Change of “condom used” to “No” as indicated in your program codes:

```
IF study=304742 AND subject=505008 and time=10 THEN excondom=1;
IF study=304742 AND subject=602006 and time=9 THEN excondom=1;
```

```
IF study = 306660 AND subject = 3065 and TIME=9 THEN excondom=1;
IF study = 306660 AND subject = 3414 and time=3 THEN excondom=1;
```

```
IF study = 306660 AND subject = 4006 AND time=3 AND (diarydt LT '10AUG04'D OR diarydt GE '13AUG04'D) THEN excondom=1;
```

```
IF study = 306660 AND subject = 4101 AND time=9 THEN excondom=1;
```

- To remove the following subjects when counting the backup days.

```
IF study = 306660 AND subject =3051 THEN delete;
IF study = 306660 AND subject =3065 THEN delete;
IF study = 306660 AND subject =3414 THEN delete;
```

```
IF study = 306660 AND subject =3674 THEN delete;
```

- To adjust the backup days to the following subjects.

```
IF study = 306660 AND subject =4006 THEN anzday=3;
```

```
IF study = 306660 AND subject =4101 THEN anzday=111;
```

- To assign “Non-compliant Cycle” to following subjects and cycles.

```
IF (subject EQ 513004 AND time GE 7)
```

```
    OR (subject EQ 606019 AND time EQ 6)
    OR (subject EQ 605007 AND time EQ 1)
    OR (subject EQ 606016 AND time EQ 4)
    OR (subject EQ 501024 AND time EQ 1)
    OR (subject EQ 503008)
    OR (subject EQ 505003 AND time EQ 5)
    OR (subject EQ 505011 AND time EQ 11)
    OR (subject EQ 508001 AND time EQ 24)
    OR (subject EQ 511016 AND time EQ 12)
    OR (subject EQ 514011 AND time IN (7,15))
    OR (subject EQ 519006 AND time GE 9)
    OR (subject EQ 519024 AND time IN (10,11))
    OR (subject EQ 601026 AND time EQ 7)
    OR (subject EQ 603005 AND time EQ 3)
    OR (subject EQ 604005 AND time EQ 14)
    OR (subject EQ 604014 AND time EQ 23)
    OR (subject EQ 604015 AND time EQ 10)
    OR (subject EQ 605013 AND time EQ 20)
```

OR (subject EQ 606005 AND time EQ 11)
OR (subject EQ 606012 AND time EQ 3)
OR (subject EQ 607011 AND time EQ 3)
OR (subject EQ 609001 AND time EQ 11)
OR (subject EQ 609002 AND time EQ 3)
OR (subject EQ 609005 AND time EQ 1)
OR (subject EQ 515008 AND time EQ 11)
OR (subject EQ 519007 AND time EQ 15)
THEN DO; nctype=5; ncspec='Non-compliant Cycle: '; END;

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

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For alternate languages please go to <http://bayerdisclaimer.bayerweb.com>

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

Qlaira

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/s/

PAMELA LUCARELLI
10/29/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communications (DDMAC)**
Attention: **Janice Maniwang 301-796-3821**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Reproductive and Urologic Drug Products (HFD-580)**
Pamela Lucarelli 301-796-3961

DATE
September 30, 2009

IND NO.

NDA NO.
22-252

TYPE OF DOCUMENT
Original

DATE OF DOCUMENT
July 6, 2009

NAME OF DRUG
Qlaira (Estradiol Valerate/Dienogest)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
March 6, 2010

NAME OF FIRM: **Bayer HealthCare Pharmaceuticals**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the labels for acceptability. The applicable labels are available through EDR. The PDUFA goal date is May 6, 2010. Please review and make recommendations by the above due date.

SIGNATURE OF REQUESTOR
Pamela Lucarelli (delivered through DARRTS)

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

ORIG-1

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Qlaira

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/s/

PAMELA LUCARELLI
09/30/2009



NDA 22-252

FILING COMMUNICATION

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Sharon W. Brown
Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Brown:

Please refer to your new drug application (NDA) dated July 2, 2009, received July 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for estradiol valerate/dienogest tablets.

We also refer to your submission dated August 11, 2009.

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 May 6, 2010.

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, mid-cycle, team, and wrap-up meetings). Please 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 April 13, 2010.

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

1. Given that the time course of estradiol in plasma after oral administration is influenced by a large pool of circulating estrone sulfate and the back conversion of estrone sulfate to estrone and estradiol, we request that you add the mean PK parameters of estrone sulfate to Table 1 in Section 12.3 of your proposed label.
2. It is noted that in Module 2 the specifications list the assay for estradiol valerate twice and do not list the assay for dienogest. The specification sheets in Module 3 are correct. Provide corrected specification sheets for Module 2.

3. Because the packaged drug product contains 5 different tablet formulations that are distinguished by color (e.g., medium vs. dark red and light vs. dark yellow), submit at least two samples of packaged drug product. These should include one batch of recently manufactured drug product and another batch of aged drug product for comparison to determine if the colors fade upon storage.
4. Submit a copy of the blister pack. Color mock-ups for the carton and immediate container labels, including any logos, should be provided to allow for full review. Ensure that SPL labeling, when submitted, contains a Drug Listing Data Elements (DLDE) table for review.

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.

Please respond only to the above requests for additional 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.

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 Pamela Lucarelli, Regulatory Health Project Manager, at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

ORIG-1

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Qlaira

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/s/

SCOTT E MONROE
09/17/2009

MEMORANDUM

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

DATE: September 9, 2009

TO: Bayer HealthCare Pharmaceuticals
Attention: Mark Rosengarten
Suzanne Hampton

FROM: Division of Reproductive and Urologic Products
Pamela Lucarelli

SUBJECT: **Statistical Information Request**
NDA 22-252, Qlaira

The following e-mail correspondence is an information request (IR) from the statistical reviewer. Please note: Attached is the e-mail correspondence, however, on July 28, 2009 I spoke with Mark Rosengarten and Suzanne Hampton via telephone and clarified the request.

Lucarelli, Pamela K

From: Lucarelli, Pamela K
Sent: Thursday, July 23, 2009 6:49 AM
To: 'Mark Rosengarten'
Subject: NDA 22-252 Statistical Question

Attachments: Request_analysis.doc

Hi Mark,

Attached is a document prepared by the statistician to aid you in the request. If you have any questions, please let me know.

Thanks,
Pam



Request_analysis.doc
(95 KB)

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

From: Lucarelli, Pamela K
Sent: Wednesday, July 22, 2009 1:21 PM
To: 'Mark Rosengarten'
Subject: NDA 22-252 Statistical Question

Hi Mark,

The statistician is looking for analysis-ready datasets in order to replicate statistical results for the following:

Contraceptive Studies 35179, 39818
DUB Studies 29849, 42568.

If you have any questions please let me know. In addition, please confirm that you have received this e-mail.

Thanks,
Pam

Pamela Lucarelli
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5323
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9897
pamela.lucarelli@fda.hhs.gov

Lucarelli, Pamela K

From: Lucarelli, Pamela K
Sent: Friday, July 24, 2009 6:54 AM
To: Fang, Xin; Mercier, Jennifer L
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Follow Up Flag: Follow up
Flag Status: Red

Xin,

I spoke with the sponsor yesterday afternoon:

1. They will provide a "proposal" on Tuesday (7/28). They want to make sure they will be providing all the information you need before they officially submit it.
2. They estimate it will take about 10 days to get everything done.
3. They will e-mail it to me and also make it an official submission.

Please let me know if you have any questions.

Thanks,
Pam

From: Fang, Xin
Sent: Thursday, July 23, 2009 3:48 PM
To: Lucarelli, Pamela K; Mercier, Jennifer L
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Dear Pam,

You are right especially under 21-century review. I think we need them before the filing meeting. Otherwise, I have to refuse to file this submission.

Thanks a lot,

Xin

From: Lucarelli, Pamela K
Sent: Thursday, July 23, 2009 2:47 PM
To: Fang, Xin; Mercier, Jennifer L
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Xin,

I think I understand - I gave you the reference (Module 5) for 'raw' SAS data, but you need analysis files to independently review the output (so you don't have to go through raw data). Correct?

Pam

From: Fang, Xin
Sent: Thursday, July 23, 2009 1:42 PM
To: Mercier, Jennifer L; Lucarelli, Pamela K
Cc: Willett, Gerald D; Sobhan, Mahboob

Subject: RE: NDA 22-252: missing analysis datasets for both indications

Dear Jen,

I am asking analysis-ready SAS datasets for OC Studies 35179, 39818, DUB Studies 29849 and 42568. I knew they submitted SAS datasets for these studies. But, those are raw/tabulation datasets. They did not submit analysis-ready datasets.

Thanks a lot,

Xin

From: Mercier, Jennifer L
Sent: Thursday, July 23, 2009 1:38 PM
To: Fang, Xin; Lucarelli, Pamela K
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Xin,

Are you asking for SAS datasets for the studies listed below?

Jen

From: Fang, Xin
Sent: Thursday, July 23, 2009 1:34 PM
To: Lucarelli, Pamela K
Cc: Willett, Gerald D; Sobhan, Mahboob; Mercier, Jennifer L
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Dear Pam,

Although the datasets they submitted to us were labeled as analysis datasets, they were actually raw/tabulation datasets. We need analysis-ready datasets which are **one-proc away** to replicate their results. In addition, we need the creating SAS programs which create the analysis-ready datasets from the submitted raw/tabulation datasets.

Thanks a lot,

Xin

From: Lucarelli, Pamela K
Sent: Thursday, July 23, 2009 1:06 PM
To: Fang, Xin
Cc: Willett, Gerald D; Sobhan, Mahboob; Mercier, Jennifer L
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Xin,

The datasets you requested for OC Studies 35179, 39818, DUB Studies 29849 and 42568 are located toward the end of Module 5 (around section 5.4) in the original submission (in EDR). The dataset is not presented as you requested, because it is not yet required. If I have misunderstood your request, please clarify.

Pam

From: Fang, Xin
Sent: Wednesday, July 22, 2009 4:13 PM
To: Lucarelli, Pamela K
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Dear Pam,

Thank you very much for your quick response. We do need analysis datasets, which are necessary for the need of many software developing here in FDA. I prepared two tables for what we need in the analysis datasets. But the sponsor is welcome to provide more information in the analysis dataset.

<< File: Request_analysis.doc >>

Regards,

Xin

From: Lucarelli, Pamela K
Sent: Wednesday, July 22, 2009 1:23 PM
To: Fang, Xin
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: RE: NDA 22-252: missing analysis datasets for both indications

Xin,

I contacted the applicant and they think they can provide a reference by tomorrow, but if they have to submit the data, they will have it to us by the filing meeting. If you have any questions, please let me know.

Thanks,
Pam

-----Original Message-----

From: Fang, Xin
Sent: Wednesday, July 22, 2009 12:19 PM
To: Lucarelli, Pamela K
Cc: Willett, Gerald D; Sobhan, Mahboob
Subject: NDA 22-252: missing analysis datasets for both indications

Dear Pamela,

In NDA 22-252, I can not find any analysis-ready dataset for us to replicate their statistical results. The analysis datasets I need are for Contraceptive Studies 35179, 39818 and for DUB Studies 29849, 42568.

Can we request them to submit the analysis datasets before filing meeting?

Thanks a lot,

Xin

-----Original Message-----

From: cderdocadmin@cder.fda.gov [<mailto:cderdocadmin@cder.fda.gov>]
Sent: Thursday, July 16, 2009 12:47 PM
To: Lucarelli, Pamela K; Yu, Chongwoo; Raheja, Krishan L; Willett, Gerald D; Fang, Xin; Mehta, Tarun; Christner, Donna; Monroe, Scott; Soule, Lisa; **Subject:** DFS Email - N 022252 N 000 02-Jul-2009 - NDA Letters

Document room update the following:

Decision Date Decision Code

N 022252 N 000 02-Jul-2009 16-Jul-2009 :

Mail paper copy to

DISTRICT OFFICE

Document Type: NDA Letters

Letter Group: Acknowledgement Letters

Letter Name: NDA Acknowledgement Letter

Submission Description: NDA 22-252 Ack Letter

Author(s)/Discipline(s)

1. Pamela Lucarelli, CSO

Signer(s)

-
1. Pamela Lucarelli
16-Jul-2009
 2. Jennifer L. Mercier
16-Jul-2009

Supervisory Signer(s)

-
1. Jennifer L. Mercier
16-Jul-2009

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

ORIG-1

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/s/

PAMELA LUCARELLI
09/09/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-252 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Qlaira Established/Proper Name: Estradiol Valerate (EV)/Dienogest (DNG) Dosage Form: Tablets Strengths: 3.0 mg EV, 2.0 mg EV and 2.0 mg DNG, 2.0 mg EV and 3.0 mg DNG, 1.0 mg EV		
Applicant: Bayer HealthCare Agent for Applicant (if applicable):		
Date of Application: July 2, 2009 Date of Receipt: July 6, 2009 Date clock started after UN:		
PDUFA Goal Date: May 6, 2009		Action Goal Date (if different):
Filing Date: September 18, 2009 Date of Filing Meeting: August 14, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1,4		
Proposed Indication(s): Prevention of pregnancy and treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception		
Type of Original NDA: AND (if applicable)		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Refer to Appendix A for further information.		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		
Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify	

Other:	clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 64,809 (b) (4)	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? **Check the Electronic Orange Book at:**
<http://www.fda.gov/cder/ob/default.htm>

YES
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL).

Comments:

All paper (except for COL)
 All electronic
 Mixed (paper/electronic)

CTD
 Non-CTD
 Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

If electronic submission:
paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

YES
 NO

Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

Comments:

If electronic submission, does it follow the eCTD guidance?
<http://www.fda.gov/cder/guidance/7087rev.pdf>

YES
 NO

If not, explain (e.g., waiver granted):

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments: A Reviewers Guide was also provided.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
PREA	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
Comments:	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments: Applicant plans to submit shortly after submission.	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: Guidance Meeting on March 17, 2004 Guidance Meeting on January 26, 2005 Guidance Meeting on July 14, 2005 Guidance Meeting on March 2, 2006</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): December 18, 2007 and February 5, 2009 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p>	<input checked="" type="checkbox"/> YES Date(s): January 16, 2007 <input type="checkbox"/> NO

Comments:	
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ATTACHMENT

MEMO OF FILING MEETING

DATE: August 14, 2009

NDA/BLA #: NDA 22-252

PROPRIETARY/ESTABLISHED NAMES: Qlaira (Estradiol Valerate/Dinogest) Tablets

APPLICANT: Bayer HealthCare Pharmaceuticals

BACKGROUND: Estradiol Valerate (EV)/Dienogest (DNG) is developed for the primary indication of prevention of pregnancy and the secondary indication of treatment of heavy/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception. The formulation is four different oral tablets containing the following: 3.0 mg EV, 2.0 mg EV and 2.0 mg DNG, 2.0 mg EV and 3.0 mg DNG and 1.0 mg EV; it will be given to women in a 26 (active)/2 (placebo) dosing regimen. This product is a New Molecular Entity (NME).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pam Lucarelli	Y
	CPMS/TL:	Jennifer Mercier	N
Cross-Discipline Team Leader (CDTL)	Lisa Soule		Y
Clinical	Reviewer:	Gerald Willett	Y
	TL:	Lisa Soule	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Project Manager:	Maria Wasilik	Y
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Chongwoo Yu	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Xin Fang	N
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Krishan Raheja	Y
	TL:	Lynnda Reid	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Tarun Mehta	Y
	TL:	Moo-Jhong Rhee Donna Christner - PAL	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:		
Other reviewers			

OTHER ATTENDEES: Scott Monroe (DRUP), Maria Walsh (ODEIII), Concepcion Cruz (MAPCB) and Kate Dwyer (DBIII)

505(b)(2) filing issues?	<input checked="" type="checkbox"/> Not Applicable
If yes, list issues:	<input type="checkbox"/> YES
	<input type="checkbox"/> NO
Per reviewers, are all parts in English or English	<input checked="" type="checkbox"/> YES

translation? If no, explain:	<input type="checkbox"/> NO
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Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable
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CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
---	--

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
---	--

<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
--	--

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
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CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
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<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Sterile product? <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Julie Beitz, Office Director</p> <p>GRMP Timeline Milestones: Receipt Date: July 6, 2009, 45 Day Filing Meeting: August 20, 2009, 74 Day Filing Letter: September 18, 2009 and PDUFA Goal Date: May 6, 2010</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input type="checkbox"/>	Send review issues/no review issues by day 74

<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

/s/

PAMELA LUCARELLI
08/24/2009

JENNIFER L MERCIER
08/25/2009



NDA 22-252

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Sharon W. Brown
Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Brown:

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: Estradiol Valerate/Dienogest Tablets

Date of Application: July 3, 2009

Date of Receipt: July 6, 2009

Our Reference Number: NDA 22-252

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 September 4, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Pamela Lucarelli, Regulatory Health Project Manager, at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
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/s/

Jennifer L. Mercier
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