

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022532Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022532

SUPPL #

HFD #

Trade Name Beyaz

Generic Name drospirenone/ethinyl estradiol and levomefolate calcium

Applicant Name Bayer HealthCare Pharmaceuticals

Approval Date, If Known September 24, 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)(2)

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# 021676

YAZ (drospirenone/ethinyl estradiol)

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 A43598 (United States) and Study A39814 (Germany)

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 A43598 (United States) and Study A39814 (Germany)

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 # 072287 YES !
! ! NO
! Explain:

Investigation #2
IND # YES !
! ! NO
! Explain:
Study conducted in Germany, IND not required

(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: September 14, 2010

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

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

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
09/24/2010

JULIE G BEITZ
09/24/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 022532 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Beyaz Established/Proper Name: drospirenone/ethinyl estradiol and levomefolate calcium Dosage Form: 3.0 mg drospirenone/0.02 mg ethinyl estradiol and 0.451 mg levomefolate calcium tablets		Applicant: Bayer HealthCare Pharmaceuticals Agent for Applicant (if applicable):
RPM: Pamela Lucarelli		Division: Division of Reproductive and Urologic Products
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Folate</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>An oral contraceptive supplemented with folate</p> <p>If no listed drug, explain.</p> <p><input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: September 24, 2010</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>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 24, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • 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>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4</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 REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<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 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<p><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</p>

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> 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 BLA: 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 checked="" 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 checked="" 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 checked="" 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 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>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	<input checked="" type="checkbox"/> Included
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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>)	Action(s) and date(s) Approved September 24, 2010
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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 draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<input checked="" type="checkbox"/> Included Final PI
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

<p>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<p>❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included Original and Final
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	<p>(b) (4) – Withdrawn December 4, 2009</p> <p>Beyaz – Approved March 9, 2010, August 13, 2010</p>
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA May 6, 2010 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC September 2, 2010, September 16, 2010 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD September 22, 2010, September 24, 2010
<p>Administrative / Regulatory Documents</p>	
<p>❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</p> <p>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</p> <p>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</p>	<input checked="" type="checkbox"/> Included October 7, 2009 <input type="checkbox"/> Not a (b)(2) September 23, 2010 <input type="checkbox"/> Not a (b)(2) September 24, 2010
<p>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</p>	<input checked="" type="checkbox"/> Included
<p>❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>	
<ul style="list-style-type: none"> • Applicant is 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
<p>❖ Pediatrics (<i>approvals only</i>)</p> <ul style="list-style-type: none"> • Date reviewed by PeRC <u>April 14, 2010</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

❖ 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 action letters), emails, faxes, telecons)</i>	<input checked="" type="checkbox"/> Included
❖ Internal memoranda, telecons, etc.	<input type="checkbox"/> Included
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg April 6, 2009
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 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 Septmeber 24, 2010
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None Septmeber 24, 2010
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None Septmeber 24, 2010
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL Review
• Clinical review(s) <i>(indicate date for each review)</i>	Septmeber 24, 2010
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See Clinical Review dated September 24, 2010 page 11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None Derm/Dental August 31, 2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None December 2, 2009, September 2, 2010, September 22, 2010
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None October 20, 2009, July 29, 2010, September 24, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None March 2, 2010, May 24, 2010, June 30, 2010
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None October 2, 2009, April 5, 2010, August 13, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> 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 checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None October 19, 2009, June 2, 2010, September 20, 2010, September 23, 2010
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <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 type="checkbox"/> None Biopharmaceutics Review Included
❖ 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>		See Product Quality Discipline Review dated June 2, 2010 p 136
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>		Date completed: May 20, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

MARIA R WALSH
09/23/2010

JULIE G BEITZ
09/23/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: September 16, 2010

To: Pam Lucarelli
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Carrie Newcomer, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 022532**
DDMAC labeling comments for Beyaz (drospirenone/ethinyl
estradiol/levomefolate calcium and levomefolate calcium) tablets

Background

This consult is in response to DRUP's September 30, 2009 request for DDMAC's review on draft labeling materials for Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium) tablets (Beyaz). DDMAC has reviewed the following draft labeling materials for Beyaz:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Patient Product Information (PPI)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on September 14, 2010. In addition, we have considered the Yaz PI (approved April 2010) (b) (4)

in our review of the draft Beyaz labeling.

We offer the following comments:

PI & PPI

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
(301) 796-3821, or janice.maniwang@fda.hhs.gov
- Carrie Newcomer (Consumer directed materials)
(301) 796-1233, or carrie.newcomer@fda.hhs.gov

30 Pages of Draft Labeling have been Withheld in Full as b4
(CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

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/s/

JANICE L MANIWANG
09/16/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY MEMO*****

Date: September 2, 2010

To: Pam Lucarelli
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 022532**
DDMAC comments on indication for Beyaz® (drospirenone/ethinyl
estradiol/levomefolate calcium tablets)

Background

DRUP has requested DDMAC's review on the indication section of the current draft product labeling (PI) on August 31, 2010. Please note that this does not constitute a complete review of the draft PI for Beyaz® (drospirenone/ethinyl estradiol/levomefolate calcium tablets) (Beyaz). We defer our complete review of the PI and PPI until a substantially complete version of the draft label is available.

We offer the following comments:

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

-



(b) (4)

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact Janice Maniwang (Professional directed materials) (301) 796-3821 or janice.maniwang@fda.hhs.gov.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
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LS INC

YAZ Folate

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/s/

JANICE L MANIWANG
09/02/2010

MEMORANDUM

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

DATE: June 24, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Thursday, June 24, 2010 4:28 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 Information Request

Hi Pam,
I have received your email below and will let you know if we have any questions.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc
Subject NDA 022532 Information Request

06/24/2010 02:35 PM

Hi Kavita,
Please submit to NDA 022532 an assessment of the impact, if any, of levomefolate calcium on the safety and efficacy of Beyaz for the treatment of acne vulgaris and premenstrual dysphoric disorder (PMDD), and final reports of any studies conducted to characterize the safety and efficacy of the proposed combination product for the treatment of acne vulgaris and PMDD.

This submission should provide adequate support for the proposed indications of acne (moderate acne for women who are at least 14 years of age, who have no known contraindication to oral contraceptive therapy and have achieved menarche. Beyaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control) and PMDD (symptoms of premenstrual dysphoric disorder in women who choose to use an oral contraceptive as their method of contraception) for your proposed combination product, Beyaz.

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

Pam

Pamela Lucarelli
Regulatory Health Project Manager

6/30/2010

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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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

YAZ Folate

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/s/

PAMELA LUCARELLI
06/30/2010

MEMORANDUM

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

DATE: May 19, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Carton/Container Labeling

APPLICATION/DRUG: NDA 022532

The correspondence below is a response to proposed carton/container labeling.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Wednesday, May 19, 2010 12:49 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 Carton/Container Labeling

Hi Pam,
I have received your email below. Thank you for providing these comments on the carton/container labeling.

We will submit the revised carton/containers and PI as quickly as possible.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc
Subject NDA 022532 Carton/Container Labeling

05/19/2010 12:44 PM

Hi Kavita,

Below is a list of comments for the proposed labeling of NDA 022532.
Kindly acknowledge receipt of this email. If you have any questions, please let me know.

Thanks,
Pam

1.  (b) (4)

5/19/2010

Thank you.

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Application
Type/Number

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Product Name

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PAMELA LUCARELLI
05/19/2010

MEMORANDUM

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

DATE: May 18, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Pharmacology Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical pharmacology information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Tuesday, May 18, 2010 1:58 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 and PRA

Pam,

I will discuss this with our Team and submit the requested letter as quickly as possible.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc
Subject NDA 022532 and (b) (4)

05/18/2010 01:55 PM

Kavita,

In the cover letter dated May 07, 2010 under response #4, you stated that an error was made (b) (4) in providing tabulated interim data (Attachment 2 to the cover letter) which showed that 122 samples were stored for > 200 days before analysis was performed. You provided a table (Attachment 1 to the cover letter) showing the list of all samples (n=70) analyzed outside of the 200 day documented stability period. Additionally, you provided a table (Attachment 3 to the cover letter) showing the errors made (b) (4) and corrections made by Sponsor.

We request that you provide a letter (b) (4) confirming the items mentioned above (refer to your Attachments 1-3) are indeed accurate with respect to the duration of sample storage prior to analysis for drospirenone. Please submit the confirmation letter to the NDA as soon as possible.

Thanks,
Pam

5/18/2010

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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ORIG-1

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LS INC

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/s/

PAMELA LUCARELLI
05/18/2010



NDA 022532

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Johal:

Please refer to your August 21, 2009 New Drug Application (NDA), received August 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for drospirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451 mg.

On April 26, 2010, we received your April 23, 2010, solicited major amendment and on May 10, 2010, we received your May 7, 2010, solicited major amendment to this application containing additional clinical and clinical pharmacology information. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 24, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 24, 2010.

If you have any questions, please 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
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

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/s/

JENNIFER L MERCIER
05/11/2010



NDA 022532

GENERAL ADVICE

Bayer HealthCare Pharmaceuticals Inc.
Attention: Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Johal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for drospirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451 mg.

Clinical Study Report A34010 included a validation report ((b) (4) Report V 7430/01) and a bioanalysis report ((b) (4) Report V 7430/02) for determination of folate metabolites in human plasma from clinical Study 309763. The validation report did not include the following stability assessments: freeze/thaw, short-term storage (e.g., at room temperature) and long-term storage (e.g., at minus 20°C or minus 70°C). In addition, it appears that at least 1 or 2 of the tested moieties (i.e., tetrahydrofolate [THF] and 5,10-methyl-THF [5,10-MTHF]) were not stable following a freeze/thaw cycle, as indicated by the results from validation Runs 2 and 3 compared to Run 1. Provide the following data as soon as possible:

1. Evidence of long-term storage stability for each tested moiety. In addition, provide a table showing the storage time (i.e., time from sample collection to time of analysis) for each study sample and whether or not it was analyzed within the demonstrated storage stability period. Samples analyzed outside of the demonstrated stability period should not be used.
2. Evidence of stability upon 3 freeze and thaw cycles for each tested moiety. In addition, provide a table showing how many freeze and thaw cycles each sample incurred prior to analysis. Given that all samples were stored at below minus 70°C upon receipt by (b) (4) all would have incurred at least 1 freeze and thaw cycle.
3. Evidence of short-term storage stability for each tested moiety. The duration of demonstrated short-term storage stability should be sufficient to cover the time allotted to process the study samples.

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
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

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JENNIFER L MERCIER
04/15/2010

MEMORANDUM

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

DATE: April 9, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: CMC Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a CMC information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Friday, April 09, 2010 2:29 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 22532 Beyaz Information Request

Hi Pam,
I have received your message below and will discuss these requests with our Team. We will respond as quickly as possible.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc
Subject NDA 22532 Beyaz Information Request

04/09/2010 02:19 PM

Hi Kavita,

Below is an CMC information request. Confirm receipt of this email. If you have any questions, please let me know.

Thanks,
Pam

1. Please provide name and address of the manufacturer and supplier of each component used in the container closure system for the drug products. If information is contained in a DMF, provide a LOA to reference the DMF.

2. Please respond to the following request that was sent in the 74-day letter: Taking into account the propensity for degradation of the levomefolate calcium, please provide the age of the clinical trial

4/9/2010

supplies to further help in the evaluation of expiration dating period and to set appropriate acceptance criteria for the degradation product.

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
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

YAZ Folate

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/s/

PAMELA LUCARELLI
04/09/2010



NDA 022532

GENERAL ADVICE

Bayer HealthCare Pharmaceuticals Inc.
Attention: Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Johal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for drospirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451 mg.

We also refer to your March 22, 2010 submission, containing a letter of authorization from (b) (4) allowing the Food and Drug Administration (FDA) to discuss with Bayer HealthCare Pharmaceuticals Inc. the findings from the Division of Scientific Investigations (DSI) inspection.

Based on the findings of the FDA DSI inspection of (b) (4), we have the following recommendations regarding the bioanalysis of samples from Study 309664:

1. Establish new calibration curves for ethinyl estradiol (EE) from 4 pg/mL to 1,000 pg/mL and re-calculate all sample concentrations using the new calibration curves with 4 pg/mL as the lower limit of quantitation (LLOQ). Bioequivalence (BE) assessment should not include any EE concentration below 4 pg/mL.
2. Establish new calibration curves for drospirenone (DRSP) from 0.5 ng/mL to 100 ng/mL and re-calculate all sample concentrations using the new calibration curve with 0.5 ng/mL as the LLOQ. BE assessment should not include any DRSP concentration below 0.5 ng/mL.
3. For BE evaluation, exclude data for DRSP from runs AQ007-03 (calibration standard failed acceptance criteria), AQ06-008 (calibration standards processed [extracted] separately from the study samples and QCs), and AQ14-003 (chromatographic interference exceeding 20% of LLOQ).
4. For BE evaluation, exclude data for DRSP from samples analyzed outside of the 200 day long-term frozen stability established in the validation experiment. Clarify how many samples were analyzed outside of the validated stability of 200 days. The report should include a table of all samples and their associated duration of long term storage prior to bioanalysis.

5. Re-evaluate the interference of blank reagent and matrix sample as well as the interference of the response of STD A and B in all runs post September 24, 2007 (these were prepared using plasma ID 5038). If the observed interference was more than 20% of the response of STD A and B in any run, reject that run.

Upon completing the recommended corrective actions, the new data set should be assessed to determine if the data are adequate to permit calculation of bioequivalence (e.g., Are there samples missing that would prevent adequate calculation of individual pharmacokinetic parameters? Is there a sufficient number of subjects remaining?). If the data set is deemed acceptable for bioequivalence assessment, BE analysis should be performed. The results of the BE analysis, PK profiles and calculated PK parameter values should be included as an amendment to Study Report A28575 and submitted to the NDA. The raw data set should also be submitted to the NDA in SAS Transport (.xpt) format. Submit the revised results and data files as soon as possible.

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
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

YAZ Folate

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/s/

JENNIFER L MERCIER
03/31/2010

MEMORANDUM

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

DATE: March 30, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Pharmacology Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical pharmacology information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Tuesday, March 30, 2010 12:42 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 22532 Information Request

Hi Pam,
I have received your email below and will discuss this request with our Team. We will respond as quickly as possible.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc
Subject NDA 22532 Information Request

03/30/2010 12:40 PM

Hi Kavita,

Below is an information request for clinical pharmacology:

Provide a response to the following information request as soon as possible.

The drospirinone (DRSP) bioanalytical report for Study 309662 states that "A matrix interference was observed in some subjects. This matrix interference was due to the use of different tubes in the clinical study. After evaluation of all results at the end of the study, it was concluded that the interference has at maximum a concentration of 1 ng/ml." Please provide the following information for study 309662.

1. A table listing all subjects with matrix interference for DRSP.
2. Clarify the nature of the matrix interference and how it was determined that the interference was due to the different tubes used in the clinical studies.

3/30/2010

3. Clarify if the samples noted as "NR" in section 16 of bioanalytical report KINE20060119 were determined to have matrix interference based on the use of a specific tube in the clinical study or was it defined by other methods? For each subject with at least one sample listed as "NR" during a treatment period, did the remaining samples in the same treatment period also have matrix interference?

4. Clarify how it was determined that the maximum interference was 1 ng/mL?

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

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 Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

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/s/

PAMELA LUCARELLI
03/30/2010



NDA 022532

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bayer HealthCare Pharmaceuticals, Inc.
PO Box 1000
Montville, New Jersey 07045-1000

ATTENTION: Kavita Johal, Pharm. D.
Assistant Director, Global Regulatory Affairs

Dear Dr. Johal:

Please refer to your New Drug Application (NDA) dated August 21, 2009 received August 24, 2009 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets 3 mg/0.02 mg/0.451 mg.

We also refer to your December 16, 2009, correspondence, received December 16, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4), and have concluded that it is acceptable and request the name be presented as Beyaz.

The proposed proprietary name, Beyaz, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 16, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Pamela Lucarelli, at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

YAZ Folate

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/s/

CAROL A HOLQUIST
03/15/2010

MEMORANDUM

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

DATE: March 2, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Pharmacology Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical pharmacology information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Tuesday, March 02, 2010 8:21 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 Clinical Pharmacology Information Request

Hi Pam,
I have received your email below. I will discuss this with our Team and let you know if we have any questions.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>

cc

Subject NDA 022532 Clinical Pharmacology Information Request

03/02/2010 08:07 AM

Kavita,

Please provide a response to the following 2 comments as soon as possible. Satisfactory response is needed to permit the use of pharmacokinetic results from study 309662.

1. The drospirenone (DRSP) bioanalytical report for study 309662 states that storage stability for DRSP in human plasma was demonstrated for 200 days. The report indicated that samples were stored for ≤ 111 days at (b) (4). However, it is not clear if samples were analyzed within 200 days from the day of sample collection (i.e., the total time stored at (b) (4) and time stored elsewhere before being shipped to (b) (4)). It appears that the first sample collected from study 309662 was on 16 August 2007 and the last analytical run for DRSP analysis was performed on 9 October 2007. Therefore the maximum storage time could be up to 419 days. Provide data supporting long term storage stability of DRSP in human plasma for at least 419 days. Alternatively, provide evidence that each sample from this study was analyzed for DRSP within 200 days of sample collection.
2. The ethinyl estradiol (EE) bioanalytical report for study 309662 states that storage stability for EE in human plasma was demonstrated for 268 days. The report indicated that samples were stored for ≤ 245 days at (b) (4). However, it is not clear if samples were analyzed within 268 days from the day of sample collection (i.e., the total time stored at (b) (4) and time stored elsewhere before

3/2/2010

being shipped to (b) (4). It appears that the first sample collected from study 309662 was on 16 August 2007 and the last analytical run for EE analysis was performed on 11 October 2007. Therefore the maximum storage time could be up to 421 days. Provide data supporting long term storage stability of EE in human plasma for at least 421 days. Alternatively, provide evidence that each sample from this study was analyzed for EE within 268 days of sample collection.

At your earliest convenience, acknowledge receipt of this email. 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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Application
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Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

YAZ Folate

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/s/

PAMELA LUCARELLI
03/02/2010

MEMORANDUM

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

DATE: February 22, 2010

TO: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Roy Blay, Ph.D., Reviewer
Division of Scientific Investigations

FROM: Pamela Lucarelli
Division of Reproductive and Urologic Products

SUBJECT: DSI Consult: Request for Clinical Inspections

APPLICATION/DRUG: NDA 022532

This memorandum is to cancel the request for a DSI GCP Consult dated December 11, 2009. No GCP Consult is required. A separate consult will be sent to GLP/BEQ.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

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LS INC

YAZ Folate

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/s/

PAMELA LUCARELLI
02/22/2010

MEMORANDUM

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

DATE: January 25, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Pharmacology Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical pharmacology information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Monday, January 25, 2010 10:35 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 Clinical Pharmacology Information Request

Hi Pam,
I have received your email below. I will discuss these comments with our Team and let you know if we have any questions. We will respond as soon as possible.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc

01/25/2010 10:09 AM

Subject NDA 022532 Clinical Pharmacology Information Request

Hi Kavita,

Per my voicemail message, below is an information request from clinical pharmacology. Please provide a response to the following 2 comments as soon as possible. Satisfactory response is needed to permit the use of pharmacokinetic results from study 309664.

1. The methyltetrahydrofolate (MTHF) bioanalytical report for study 309664 states that the maximum duration of sample storage (from first collection date to last analysis) was 335 days. It further states that stability of MTHF in human serum at -20 °C and -80 °C was demonstrated for 286 days and that stability study will be extended to cover the study sample storage period. Provide data supporting long term storage stability of MTHF in human serum for at least 335 days. Alternatively, provide evidence that each sample from this study was analyzed for MTHF within 286 days of sample collection.

1/25/2010

2. The drospirenone (DRSP) bioanalytical report for study 309664 states that storage stability for DRSP in human plasma was demonstrated for 200 days. The report indicated that all reported values were based on sample stored for ≤ 200 days at (b) (4) (except for one sample from subject 8 that were analyzed on 25 October 2007, which was stored for 205 days at (b) (4)). It is not clear if samples were analyzed within 200 days from the day of sample collection (i.e., the total time stored at (b) (4) and time stored elsewhere before being shipped to (b) (4)). It appears that the first sample collected from study 309664 was on 8 January 2007 and the last analytical run for DRSP analysis was performed on 25 October 2007. Therefore the maximum storage time could be up to 290 days. Provide data supporting long term storage stability of DRSP in human plasma for at least 290 days. Alternatively, provide evidence that each sample from this study was analyzed for DRSP within 200 days of sample collection.

If you have any questions please let me know. Additionally, 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

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	YAZ Folate

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/s/

PAMELA LUCARELLI
01/25/2010

MEMORANDUM

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

DATE: January 25, 2010

TO: Bayer HealthCare Pharmaceuticals, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Monday, January 25, 2010 2:10 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 Clinical Information Request

Hi Pam,
I have received your email below. I will discuss these items with our Team and let you know if we have any questions.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Lucarelli, Pamela K" <Pamela.Lucarelli@fda.hhs.gov>, "Kavita Johal"
<kavita.johal@bayer.com>

cc

01/25/2010 01:06 PM

Subject NDA 022532 Clinical Information Request

[Correction to the subject line - this is NDA 022532.](#)

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

1/25/2010

pamela.lucarelli@fda.hhs.gov

From: Lucarelli, Pamela K
Sent: Monday, January 25, 2010 1:04 PM
To: 'Kavita Johal'
Subject: NDA 022252 Clinical Information Request

Hi Kavita,

Below is a clinical information request for NDA 022532 pertaining to your invalid samples.

These first items are specific to Study A43598

1. Characterize specifically the sample handling and sample preparation errors discovered in this trial (e.g., incorrect sample dilution), and clarify whether these have been confirmed to have occurred by study site personnel.
2. Provide a listing of all RBC Folate values that were excluded on the basis of invalid or implausible hemoglobin or hematocrit, organized by subject ID, treatment arm, site and visit.
3. Provide a tabulation of number of samples excluded by reason for exclusion for each study site, by treatment arm.
4. Provide the reasons leading to "invalid" codes for data from sites other than 104 and 108 (as well as for any data from Sites 104 and 108 that were excluded for reasons other than sample handling errors).
5. Clarify whether "Scenario B" excluded all data from Sites 104 and 108, or only data flagged as invalid.

For both Studies A39814 and A43598, the baseline values for the plasma and RBC folate levels were based on the data from three pre-treatment visits.

Clarify why the average of the three values was used for Study A39814 while the median of the three values was used for Study A43598.

If you have any questions about this information request, please let me know. Additionally, verify 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

1/25/2010

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NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	YAZ Folate

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PAMELA LUCARELLI
01/25/2010

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, Kavita Johal, Pharm. D

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Clinical Pharmacology Information Request

APPLICATION/DRUG: NDA 022532

The correspondence below is a clinical pharmacology information request.

Lucarelli, Pamela K

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Tuesday, January 05, 2010 11:57 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022532 Information Request

Hi Pam,
Happy New Year to you!

I have received your email below and will discuss with our Team as soon as possible.

Thanks.

Best regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's HealthCare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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

To "Kavita Johal" <kavita.johal@bayer.com>
cc
Subject NDA 022532 Information Request

01/05/2010 11:02 AM

Hi Kavita,

Below is an information request from clinical pharmacology:

Please add the following columns to the data file named KINMS01.XPT for studies A28575 (protocol 309664) and A27410 (protocol 309662)

1. Time (in hours relative to time of dosing)
2. Treatment administered
3. Baseline corrected concentration

Please add the following column to the data file named KINCAL01.XPT for studies A28575 (protocol 309664) and A27410 (protocol 309662)

1. Treatment administered

1/5/2010

Submit the new files as soon as possible.

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

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
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22532

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

YAZ Folate

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/s/

PAMELA LUCARELLI
01/05/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022532

MEETING MINUTES

Bayer Health Care Pharmaceuticals Inc.
PO Box 1000
Montville, New Jersey 07045-1000

Attention: Ms. Kavita Johal,
Assistant Director, Global Regulatory Affairs

Dear Ms. Kavita:

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

We also refer to the telecon between representatives of your firm and the FDA on November 19, 2009. The purpose of the meeting was to discuss the review of the proprietary name (b) (4).

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

If you have any questions, call Maria Wasilik, Safety Regulatory Project Manager at (301) 796-0567.

Sincerely,

{See appended electronic signature page}

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



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Teleconference with Bayer HealthCare Pharmaceuticals
Meeting Category: NDA

Meeting Date and Time: November 19, 2009 10:45 A.M.
Meeting Location: WO Conference Room 5313

Application Number: 022532
Product Name: (b) (4)
Indication: Oral contraceptive
Sponsor/Applicant Name: Bayer HealthCare Pharmaceuticals, Inc.

Meeting Chair: Kellie Taylor, FDA
Meeting Recorder: Maria Wasilik, FDA

FDA ATTENDEES:

Maria Wasilik, Safety Regulatory Project Manager, OSE
Doris Bates, Team Leader Safety Regulatory Project Management, OSE
Melina Griffis, Team Leader, DMEPA
Richard Abate, Safety Evaluator, DMEPA
Kellie Taylor, Team Leader, DMEPA
Pamela Lucarelli, Project Manager, DRUP
Lisa Soule, Medical Officer, DRUP
Daniel Davis, Medical Officer, DRUP

SPONSOR ATTENDEES

Sharon Brown, Director, Global Regulatory Affairs
Kavita Johal, Assistant Director, Global Regulatory Affairs
Joachim Marr, Vice President, Global Clinical Development
Carole Sampson-Landers, Director, Global Clinical Development
Leo Plouffe, Vice President, Medical Affairs
Richard Lynen, Deputy Director, Medical Affairs
Leslie North, Vice President, Marketing
Samer Lezzaiq, Director, Marketing
Bettina Fiedler, Head of Global Regulatory Affairs Women's Healthcare

1.0 BACKGROUND

DMEPA has completed an evaluation of the proposed proprietary name, (b) (4) and has objections to the proposed name for the following reasons.

(b) (4)

The purpose of this meeting was to explain FDA's concerns with the tradename.

2. DISCUSSION

As stated in the background information, DMEPA explained the reasons for objecting to the tradename. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

DMEPA then conveyed possible options for moving forward:

1. The sponsor can withdraw the proposed tradename (b) (4), and resubmit a new proposed tradename, which would get a new 90 day review clock.

2. FDA would issue a letter to the sponsor indicating that the proposed tradename, (b) (4), is unacceptable. This would occur on or around December 24, 2009 (OSE's PDUFA date for the tradename review).
3. The sponsor can consider submitting a different modifier as a prefix or suffix. Data to support any new modifier should be included with the new submission.

Bayer stated that they understand DMEPA's recommendation to withdraw and submit a new name and asked about submitting two new names at once. DMEPA clarified that they do not conduct concurrent reviews on multiple names. However, if two names are submitted, both will be reviewed concurrently by DDMAC for promotional issues. DMEPA will then review the second name, if the first one is found unacceptable. Whether the first or second name in the new tradename submission is reviewed by DMEPA in this scenario, a new 90-day review clock would start based on the date the new submission is received.

Bayer inquired about the possibility of teleconference(s) with OSE via during the review of the second name. FDA will communicate up front as much as possible if we identify significant issues and resources allow.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

The sponsor will follow up with OSE Safety Regulatory Project Manager, Maria Wasilik.

5.0 ATTACHMENTS AND HANDOUTS

None.

Application
Type/Number

Submission
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Submitter Name

Product Name

NDA-22532

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/s/

KELLIE A TAYLOR
12/09/2009



NDA 22-532

FILING COMMUNICATION

Bayer HealthCare Pharmaceuticals Inc.
Attention: Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Johal:

Please refer to your new drug application (NDA) dated August 21, 2009, received August 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for drospirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451 mg.

We also refer to your submission dated September 29, 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 June 24, 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, midcycle, 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 May 24, 2010.

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

1. Because of the propensity for degradation of levomefolate calcium, provide the age of the clinical trial supplies to further assist us in evaluation of the proposed expiration dating period and in setting an appropriate acceptance criteria for degradation products.
2. Clarify whether the original or normalized red blood cell folate values were used for the primary efficacy analysis in Study A43598.
3. Provide the name of the SAS dataset and variables within the dataset used for the primary efficacy analysis in Study A43598. Also, provide the SAS code for the analysis.

4. Submit the corresponding datasets to support your population PK/PD analysis of Metafolin in the report A47012:
 - All datasets used for model development (corresponding to your NONMEM codes directly) and validation should be submitted in SAS transport file (*.xpt) format. A description of each data item should be provided in a define.pdf file. Any data points and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
 - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

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 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-22532

ORIG-1

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/s/

SCOTT E MONROE
11/06/2009

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.
22-532

TYPE OF DOCUMENT
Original

DATE OF DOCUMENT
August 24, 2009

NAME OF DRUG
(b) (4)

(drospirenone/ethinyl estradiol/levomefolae calcium)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
May 24, 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 June 24, 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-22532

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/s/

PAMELA LUCARELLI
09/30/2009

David, Jeannie C

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Tuesday, September 29, 2009 4:48 PM
To: David, Jeannie C
Cc: Deborah Flint; Mike Koenig; Robert Kelly
Subject: NDA 22-532: FDA Request #3 re: CMC establishment information (FDA Form 356 h) - 4 additional questions
Attachments: NDA 22-532_356h Continuation Page_Response to FDA Request.doc

Dear Jeannie,

In follow-up to your voice message from yesterday, please find below responses to your questions, as well as, updated continuation pages for the Form FDA 356h. An updated Form FDA 356 was planned for submission today; however, it has taken us time to receive the appropriate information from our Berlin colleagues so this submission will be made tomorrow.

Secondary Packaging Sites - The Form FDA 356h continuation pages have been updated to reflect these secondary packaging sites, as well as, the contact information for the secondary packaging sites.

Labeling - The Berlin site is responsible for Labeling. I apologize for this error provided in our previous response.

Weimar Site Functions -

- Manufacturing of bulk tablets
- QC release testing of bulk tablets
- QC stability testing of final packaged/labeled product*

* Following packaging/labeling at Berlin finished drug product is sent to Weimar for inclusion into the stability testing program (retain samples maintained at Berlin)

Bergkamen (Drug Substance) Site - The Form FDA 35h continuation pages have been updated to reflect exactly what drug substance are dealt with at what site.

Berlin responsible for the following:

- Final packaging of product
- Final labeling of product
- Release of marketed product

Wayne is responsible for the following:

- Administrative (paper) release of final product

9/29/2009

If you have any additional questions on the continuation pages, please let me know so we can address them in tomorrow's submission.

For future CMC-related inquiries, you may contact my CMC-RA colleagues listed below.

Deborah Flint, Associate Director, CMC Regulatory Affairs

Phone: 973-487-2483

Email: deborah.flint@bayer.com

Michael Koenig, Associate Director, CMC Regulatory Affairs

Phone: 973-305-5442

Email: mike.koenig@bayer.com

Robert Kelly, Director CMC & Marketed Products

Phone: 973-487-2161

Email: robert.kelly@bayer.com

Thanks.

Best Regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's Healthcare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

9/29/2009

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JEANNIE C DAVID
09/29/2009

MEMORANDUM

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

DATE: 9/28/09, 9:30 am

TO: Kavita Johal, Assistant Director, Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc., Ph: 973-487-2078

THROUGH : Jeannie David, Regulatory Project Manager, ONDQA

FROM: Jeannie David, Regulatory Project Manager, ONDQA

SUBJECT: Memo of Telecon: Request for clarification on establishments information

APPLICATION/DRUG: NDA 22-532 / drospirenone/ethinylestradiol/levomefolate calcium
Tablets

****Memo of Telecon:**

The following clarifications were requested in a telephone conversation from Jeannie David, RPM, ONDQA, to Kavita Johal, Bayer, regarding establishment information submitted to the original NDA on Form FDA 356h - Continuation Page:

1. Clarify inconsistencies in telephone numbers and fax numbers provided for Dr. Hans-Joachim Raubach listed in the Drug Substance (p. 2/3) and Drug Product (p. 3/3) sections. Confirm the appropriate contact for each of the sites for which Dr. Raubach is listed.
2. Elaborate on "Release for distribution" listed for the Bayer, Wayne, NJ site. Indicate whether or not additional testing, repackaging, labeling/relabeling, storage for stability or retain samples, or opening of the product for any reason occurs at this site. Otherwise, state if only administrative functions occur at the site.
3. Indicate where labeling operations for the Drug Product occur.

****Post Telecon Note:**

An email of responses from the applicant to these 3 requests was received on 9/28/09, attached.

David, Jeannie C

From: Kavita Johal [kavita.johal@bayer.com]
Sent: Monday, September 28, 2009 1:45 PM
To: David, Jeannie C
Subject: NDA 22-532: Response to Request for Information (FDA Request #3) re: CMC establishment information (FDA Form 356 h continuation pages)

Dear Jeannie,

In follow-up to our discussion this morning, please find below responses to your questions regarding the Form FDA 356h continuation pages submitted for NDA 22-532.

Contact Information for Dr. Hans-Joachim Raubach

Dr. Hans-Joachim Raubach is the correct contact person for the Drug Substance and also the contact person for the Drug Product. His telephone number is 011 49 30 4681 6826.
His fax number is 011 49 30 4689 6826.

Clarification regarding Wayne, NJ site

The Wayne, NJ site "Release to Distribution" is only an administrative site. There are no technical operations being performed (i.e. testing, re-packaging, labeling, opening of products, storing for stability, retaining samples for future stability studies) at this site.

Labeling

The labeling operations for the Drug Product are being performed at the Weimar Plant in Weimar, Germany.

Please let me know if the above clarifies your questions and if you have any additional questions. A revised Form FDA 356h will be submitted to the NDA.

Thanks.

Best Regards,
Kavita

Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
Women's Healthcare

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000
Phone: 973-487-2078
Fax: 973-487-2016
Email: kavita.johal@bayer.com

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9/28/2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	YAZ

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/s/

JEANNIE C DAVID
09/28/2009

MEMORANDUM

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

DATE: 9/28/09, 4:00 pm

TO: Kavita Johal, Assistant Director, Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc., Ph: 973-487-2078

THROUGH : Jeannie David, Regulatory Project Manager, ONDQA

FROM: Jeannie David, Regulatory Project Manager, ONDQA

SUBJECT: Memo of Telecon: 2nd request for clarification on establishments information

APPLICATION/DRUG: NDA 22-532 / drospirenone/ethinylestradiol/levomefolate calcium
Tablets

**Memo of Telecon:

The following clarifications were requested in a second telephone conversation from Jeannie David, RPM, ONDQA, to Kavita Johal, Bayer, regarding establishment information submitted to the original NDA on Form FDA 356h - Continuation Page, and an email response on 9/28/09 from Kavita Johal to Jeannie David:

1. Clarify if the 3 secondary drug product packaging sites listed in Modules 2 and 3 are relevant to the NDA. If so, include this information in the Form FDA 356h - Continuation Page, along with complete contact information.
2. Clarify how labeling operations for the Drug Product are being performed at the Weimar Plant in Weimar, Germany, as stated in an 9/28/09 email from Kavita Johal to Jeannie David, when this is the site for drug product manufacturing and testing, and the primary packaging and secondary packaging occur at separate sites. Identify all site(s) for direct product labeling and secondary packaging labeling.
3. Elaborate on the "Quality control" function listed for the Weimar Plant in Weimar, Germany in Modules 2 and 3. Does this include release testing? Does this include other testing?

The applicant responded that she will follow up on these 3 points within the next day, and arrange a brief telecon with chemistry regulatory affairs if needed to expedite the clarifications.

The applicant will hold on amending the Form FDA 356h - Continuation Page until these additional issues are resolved, and will submit all final changes as a formal amendment to the NDA.

A fourth point was added in a voicemail from Jeannie David to Kavita Johal, 9/28/09, 4:40pm:

4. It is noted that the drug substance levomefolate calcium is manufactured at Merck Eprova AG in Schafhausen, Switzerland. Bayer Schering Pharma AG site in Bergkamen, Germany, is listed as manufacturing and testing for "drug substances." Clarify which drug substances are being manufactured at the Bergkamen, Germany site.

Application
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Submission
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Submitter Name

Product Name

NDA-22532

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JEANNIE C DAVID
09/28/2009



NDA 22-532

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals Inc.
Attention: Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Johal:

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: dropirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium
0.451 mg

Date of Application: August 21, 2009

Date of Receipt: August 24, 2009

Our Reference Number: NDA 22-532

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 October 23, 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.

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
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
08/27/2009