

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022574Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022574

SUPPL #

HFD #

Trade Name Safyral

Generic Name drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets

Applicant Name Bayer HealthCare Pharmaceuticals, Inc.

Approval Date, If Known December 16, 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?

3

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# 022532 Beyaz

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), Study A39814 (Germany) and Study A27410 (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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

NDA 022532 Beyaz

- 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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

Investigation #1 !
!
YES ! NO
Explain: ! Explain:
The applicant provided support for
the study

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

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

YES NO

If yes, explain:

=====

Name of person completing form: Pam Lucarelli
Title: Regulatory Health Project Manager
Date: December 8, 2010

Name of Office/Division Director signing form: Scott Monroe
Title: Division Director

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

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/s/

PAMELA LUCARELLI
12/16/2010

SCOTT E MONROE
12/16/2010



1.4.4 Cross reference to other applications

Bayer HealthCare Pharmaceuticals permits the Division to access the applications listed below that contain supporting information on drospirenone/ethinyl estradiol (DRSP/EE) tablets and levomefolate calcium (Metafolin[®]) tablets for this New Drug Application.

DRSP 3 mg/EE 0.03 mg tablets:

IND 51,693

IND 53,905

NDA 21-098 (Yasmin[®])

DRSP 3 mg/EE 0.02 mg tablets:

IND 60,738 (OC indication)

IND 65,370

NDA 21-676 (Yaz[®])

DRSP 3 mg/EE 0.02 mg tablets + Levomefolate Calcium 0.451 mg tablets:

NDA 22-532

Levomefolate Calcium 0.451 mg tablets:

IND 72,287



Bayer Healthcare Pharmaceuticals hereby certifies under FD&C Act, Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this drug product application.

Date:

Signature:

A handwritten signature in black ink, appearing to read "John Talian".

John Talian, PhD

Vice President, Global Regulatory Affairs

Head of US Regulatory Affairs

Bayer HealthCare Pharmaceuticals

MEMORANDUM

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

DATE: December 15, 2010

TO: Division of Reproductive and Urologic Products, Pamela Lucarelli

FROM: Division of Medication Error Prevention and Analysis, Anne Crandall

SUBJECT: Carton and Container Labeling

APPLICATION/DRUG: NDA 022574

The correspondence below is regarding carton and container labeling for NDA 022574.

Lucarelli, Pamela K

From: Crandall, Anne
Sent: Wednesday, December 15, 2010 10:43 AM
To: Lucarelli, Pamela K; Wasilik, Maria
Subject: RE: NDA 022574 Carton and Container Labeling

DMEPA concurs with CMC regarding the acceptability of the carton and container labeling for NDA 022574.

~~~~~  
Anne Crandall Tobenkin, PharmD.  
Safety Evaluator  
FDA/CDER/OSE/Division of Medication Error Prevention and Analysis  
10903 New Hampshire Ave. Mail Stop 4447  
Silver Spring, MD 20993  
Building #22, Rm 4465  
Phone number: 301-796-2282

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**From:** Lucarelli, Pamela K  
**Sent:** Tuesday, December 14, 2010 8:21 AM  
**To:** Crandall, Anne; Wasilik, Maria  
**Subject:** NDA 022574 Carton and Container Labeling

Anne and Maria,

Your August 27th review in DARRTS defers to ONDQA regarding the acceptability of the carton and container labeling. CMC finds it acceptable, did you plan to enter something else in DARRTS?

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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/s/  
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PAMELA LUCARELLI  
12/15/2010

**505(b)(2) ASSESSMENT**

| <b>Application Information</b>                                                                                                                                                                                                                                                                                    |                                  |                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------------|
| NDA # 022574                                                                                                                                                                                                                                                                                                      | NDA Supplement #: S-             | Efficacy Supplement Type SE- |
| Proprietary Name: Safyral<br>Established/Proper Name: drospirenone/ethinyl estradiol/levomefolate calcium<br>Dosage Form: tablets<br>Strengths: drospirenone 3 mg/ethinyl estradiol 0.03 mg/levomefolate calcium 0.451 mg                                                                                         |                                  |                              |
| Applicant: Bayer HealthCare                                                                                                                                                                                                                                                                                       |                                  |                              |
| Date of Receipt: November 16, 2009                                                                                                                                                                                                                                                                                |                                  |                              |
| PDUFA Goal Date: December 16, 2010                                                                                                                                                                                                                                                                                | Action Goal Date (if different): |                              |
| Proposed Indication(s): Safyral is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product. |                                  |                              |

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling)                                              |
|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Published Literature                                                            | Clinical Trials Section: Information regarding the potential of folate supplementation to reduce the risk of neural tube defects |
|                                                                                 |                                                                                                                                  |
|                                                                                 |                                                                                                                                  |

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The potential to reduce the incidence of neural tube defects (NTDs) with folate supplementation is well established based on a body of evidence derived from randomized, controlled trials, nonrandomized intervention trials, and observational studies using folic acid. Therefore, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily. RBC and plasma folate levels were measured in StudyA39814 for Safyral.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

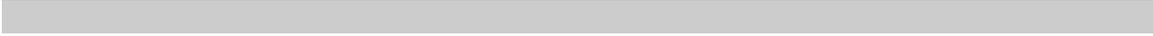
- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO”, proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Drug | NDA/ANDA # | Did applicant specify reliance on the product? (Y/N) |
|--------------|------------|------------------------------------------------------|
|              |            |                                                      |
|              |            |                                                      |

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

**(Pharmaceutical equivalents** are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

**Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES  NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 022532 Beyaz

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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PAMELA LUCARELLI  
12/07/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022574

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Robert J. Haydu  
Deputy Director, Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Mr. Haydu:

Please refer to your November 16, 2009, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for drospirenone 3.0 mg/ethinyl estradiol 0.03 mg and levomefolate calcium 0.451 mg tablet.

On August 27 and September 3, 2010, we received your solicited major amendments to this application. The receipt dates are 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 submissions. The extended user fee goal date is December 16, 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 November 16, 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

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NDA-22574

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ORIG-1

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BAYER CORP  
PHARMACEUTICA  
L DIV

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YASMIN PLUS  
(DEOSPIRENONE ETHINYL  
ESTRAD

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/s/  
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JENNIFER L MERCIER

09/08/2010



NDA 022574

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Robert J. Haydu,  
Deputy Director, Regulatory Affairs

Dear Mr. Haydu:

Please refer to your New Drug Application (NDA) dated November 16, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg.

We also refer to your August 12, 2010, correspondence, received August 12, 2010, requesting review of your proposed proprietary name, Safyral. We have completed our review of the proposed proprietary name, Safyral and have concluded that it is acceptable.

The proposed proprietary name, Safyral, 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 August 12, 2010 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}*

Denise P. Toyer, PharmD

Deputy 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

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NDA-22574

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/s/  
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DENISE P TOYER  
08/27/2010

**MEMORANDUM**

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

**DATE:** August 20, 2010

**TO:** Bayer HealthCare Pharmaceuticals, Robert Haydu

**FROM:** Division of Reproductive and Urologic Products, Pamela Lucarelli

**SUBJECT: Clinical Pharmacology Information Request**

**APPLICATION/DRUG:** NDA 022574

The correspondence below is a clinical pharmacology information request.

## Lucarelli, Pamela K

---

**From:** Robert Haydu [robert.haydu@bayer.com]  
**Sent:** Friday, August 20, 2010 12:29 PM  
**To:** Lucarelli, Pamela K  
**Subject:** Re: NDA 022574 Information Request

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

Best Regards

Bob

---

Robert Haydu  
Deputy Director, Regulatory Affairs  
CMC Marketed Products

Bayer HealthCare Pharmaceuticals Inc.  
P.O. Box 1000  
Montville, NJ 07045-1000  
Phone: +1 973-487-2411  
Fax: +1 973-487-2016  
E-mail: robert.haydu@bayer.com

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

08/20/2010 11:22 AM

To "Robert Haydu" <robert.haydu@bayer.com>  
cc "Sharon Brown" <sharon.brown@bayer.com>  
Subject NDA 022574 Information Request

Hi Bob,

Below is an information request from our clinical pharmacology reviewer.

8/20/2010

Based on the findings of the FDA DSI inspection of (b) (4) we have the following recommendations regarding the bioanalysis of samples from Study 309662:

1. Establish new calibration curves for ethinyl estradiol (EE) from 4 pg/mL to 1,000 pg/mL and recalculate 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 recalculate 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. There were inconsistencies in deciding when an assay was conducted due to internal standard variability that affected 3 samples. Replace the "original result" values with the new "reported result" values for the 3 affected samples as shown in the table below. BE assessment should use the values as indicated under the "reported result" column for these samples.

| ID   | Sample ID                   | Original result | Reported result | Comment                                                                                                                                                                    |
|------|-----------------------------|-----------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0819 | PID 3, Period 3, 8 hr       | 36.5 pg/mL      | 32.4 pg/mL      | Result from run AQ17-002 is reported, because this run is accepted upon rejection of STD A. Low IS was observed in run AQ17-008 (reanalysis run, now unnecessary analysis) |
| 1059 | PID 12, Period 2, - 0.50 hr | <LLQ            | <4.00 pg/mL     | Was reanalysed at the time                                                                                                                                                 |
| 1735 | PID 26, Period 2, 4 hr      | 30.2 pg/mL      | NR              | Set to NR as a result of applying the new 30-170% rule.                                                                                                                    |

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 A27410 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.

Confirm 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  
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Submission  
Type/Number

Submitter Name

Product Name

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NDA-22574

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/s/  
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PAMELA LUCARELLI

08/20/2010



NDA 022574

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

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

ATTENTION: Robert J. Haydu  
Deputy Director, Regulatory Affairs

Dear Mr. Haydu:

Please refer to your New Drug Application (NDA) dated November 16, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg.

We acknowledge receipt of your August 12, 2010, correspondence, received on August 12, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of August 12, 2010.

We also acknowledge the receipt of your August 12, 2010, correspondence requesting a review of your proposed proprietary name, Safyral.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, 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-22574               | ORIG-1                 | BAYER CORP<br>PHARMACEUTICA<br>L DIV | YASMIN PLUS<br>(DEOSPIRENONE ETHINYL<br>ESTRAD |

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/s/

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MARIA R WASILIK  
08/13/2010

CAROL A HOLQUIST  
08/13/2010

**MEMORANDUM**

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

**DATE:** July 26, 2010

**TO:** Bayer HealthCare Pharmaceuticals, Robert Haydu

**FROM:** Division of Reproductive and Urologic Products, Pamela Lucarelli

**SUBJECT: Biopharmaceutics Information Request**

**APPLICATION/DRUG:** NDA 022574

The correspondence below is a biopharmaceutics information request.

**Lucarelli, Pamela K**

---

**From:** Robert Haydu [robert.haydu@bayer.com]  
**Sent:** Monday, July 26, 2010 3:07 PM  
**To:** Lucarelli, Pamela K  
**Subject:** Re: NDA 022574 Comment to Applicant  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

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

Best Regards

Bob

---

Robert Haydu  
 Deputy Director, Regulatory Affairs  
 CMC Marketed Products

Bayer HealthCare Pharmaceuticals Inc.  
 P.O. Box 1000  
 Montville, NJ 07045-1000  
 Phone: +1 973-487-2411  
 Fax: +1 973-487-2016  
 E-mail: robert.haydu@bayer.com

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

To "Robert Haydu" <robert.haydu@bayer.com>  
 cc  
 Subject NDA 022574 Comment to Applicant

07/26/2010 02:28 PM

Hi Bob,

Please see the comment below from our biopharmaceutics team.

The following dissolution method and specifications are recommended for  
 Drospirenone + Ethinylestradiol + Levomefolate calcium coated tablet 3.0 mg + 0.03 mg +  
 0.451 mg based on the mean dissolution values from batches used in pivotal clinical  
 trials and drug product stability:

| Dosage Form | USP Apparatus | Speed (rpm) | Medium | Volume (mL) | Specification |
|-------------|---------------|-------------|--------|-------------|---------------|
|-------------|---------------|-------------|--------|-------------|---------------|

7/28/2010

IR tablet II (Paddle) 50 phosphate buffered saline pH 6.8 containing 0.03 % ascorbic acid 900 No  
less than (b) (4) (Q) of the labeled amount of each active ingredient  
(drospirenone,  
ethinylestradiol, and  
levomefolate calcium) is  
dissolved in 15 min.

Please revise the dissolution specifications accordingly.

Please acknowledge receipt of this email. If you have any questions, 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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Product Name

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NDA-22574

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/s/  
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PAMELA LUCARELLI

07/28/2010



NDA 022574

**FILING COMMUNICATION**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Robert J. Haydu  
Associate Director, Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Mr. Haydu:

Please refer to your new drug application (NDA) dated and received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for drospirenone 3.0 mg/ethinyl estradiol 0.03 mg and levomefolate calcium 0.451 mg tablet.

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 September 16, 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 August 9, 2010.

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

1. Taking into account the propensity for degradation of the levomefolate calcium, provide the age of the clinical trial supplies to further help us in the evaluation of the proposed expiration dating period and in setting an appropriate acceptance criteria for degradation products.
2. Submit a report of your dissolution method development and validation. These data should also include tabulated values of individual and mean percent dissolved under the conditions tested.

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

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/s/  
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SCOTT E MONROE  
01/27/2010

**REQUEST FOR DDMAC LABELING REVIEW CONSULTATION**

**\*\*Please send immediately following the Filing/Planning meeting\*\***

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

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

REQUEST DATE  
January 14, 2010

IND NO.

NDA/BLA NO.  
NDA 022574

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)  
See Below

NAME OF DRUG  
drospirenone/ethinyl  
estradiol/levomefolate calcium

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)  
July 1, 2010

NAME OF FIRM:  
Bayer HealthCare

PDUFA Date: September 16, 2010

**TYPE OF LABEL TO REVIEW**

**TYPE OF LABELING:**

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

**TYPE OF APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING
- LABELING REVISION

**EDR link to submission:**

<\\CDSESUB1\EVSPROD\NDA022574\022574.ENX>

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: April 19, 2010

Labeling Meetings: July 7, 2010 and July 22, 2010

Wrap-Up Meeting: July 7, 2010

SIGNATURE OF REQUESTER  
Pamela Lucarelli (delivered through DARRTS)

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

- eMAIL
- HAND

**DSI CONSULT**  
**Request for Biopharmaceutical Inspections**

**DATE:** January 13, 2010

**TO:** Associate Director for Bioequivalence  
 Division of Scientific Investigations, HFD-48

**THROUGH:** E. Dennis Bashaw, Pharm.D.  
 Director, Division of Clinical Pharmacology III, Office of Clinical Pharmacology

**FROM:** Pamela Lucarelli, Regulatory Health Project Manager, HFD-580

**SUBJECT: Request for Biopharmaceutical Inspections**  
 NDA 022574  
 drospirenone 3 mg, ethinyl estradiol 0.03 mg, levomefolate calcium 0.451 mg

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

| Study #                                         | Clinical Site (name, address, phone, fax, contact person, if available)                                                                                                                           | Analytical Site (name, address, phone, fax, contact person, if available)                                                                      |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Protocol #<br>309662<br>(Study report # A27410) | <b>Principal Investigators:</b><br>A. Port<br>U. Eydeler<br>Scope International Life Sciences AG<br>Frohboesestraße 12-14<br>D-22525 Hamburg (Germany)<br><br><b>Co-investigators:</b><br>(b) (4) | <u>For drospirenone and ethinyl estradiol:</u><br>(b) (4)<br>[Redacted]<br><br><u>For L-5-methyltetrahydrofolate:</u><br>(b) (4)<br>[Redacted] |

**International Inspections:**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain): Pivotal bioequivalence study.

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **June 1, 2010**. We intend to issue an action letter on this application by **September 16, 2010**.

Should you require any additional information, please contact Pamela Lucarelli, Regulatory Health Project Manager at (301) 796-3961.

Concurrence:

Myong Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)

Doanh Tran, Ph.D. – Clinical Pharmacology Reviewer, DCPIII, OCP

| Application Type/Number | Submission Type/Number | Submitter Name                       | Product Name                                   |
|-------------------------|------------------------|--------------------------------------|------------------------------------------------|
| NDA-22574               | ORIG-1                 | BAYER CORP<br>PHARMACEUTICA<br>L DIV | YASMIN PLUS<br>(DEOSPIRENONE ETHINYL<br>ESTRAD |

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/s/

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PAMELA LUCARELLI  
01/13/2010

EDWARD D BASHAW  
01/13/2010



NDA 022574

**NDA ACKNOWLEDGMENT**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Robert J. Haydu  
Associate Director, Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Mr. Haydu:

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: drosiprenone 3.0 mg/ethinyl estradiol 0.03 mg and levomefolate calcium 0.451 mg

Date of Application: November 16, 2009

Date of Receipt: November 16, 2009

Our Reference Number: NDA 022574

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 January 15, 2010, in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

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

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

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NDA-22574

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JENNIFER L MERCIER

12/01/2009