

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022574Orig1s000

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22-574
APPLICANT	Bayer Healthcare Pharmaceuticals
DRUG NAME	SAFYRAL (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
SUBMISSION DATE	16 November 2009
PDUFA DATE	16 December 2010
SEALD SIGN-OFF DATE	16 December 2010
OND ASSOCIATE DIRECTOR FOR LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies found in the SEALD Labeling Review filed 13 December 2010, for this application have been addressed. SEALD agrees that the PI is ready for approval at this time.

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/s/

ANN M TRENTACOSTI
12/16/2010
Signing for Laurie Burke

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022574
APPLICANT	Bayer Healthcare Pharmaceuticals
PRODUCT NAME	Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
SUBMISSION DATE	11/16/2009
PDUFA DATE	12/16/2010
SEALD REVIEW DATE	12/13/2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information

For other regulatory requirements, see 21 CFR 201.56 and 201.57.

Highlights (HL)

- **General comments**

- Highlights is in 8-point font, two-column format, with ½ inch margins.
- Highlights is limited in length to one-half page. If greater than one-half page, a waiver has been granted previously or has been requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and TOC
- All headings must be presented in the center of a horizontal line in upper-case letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
Please cite 6.1 in the Adverse Reactions section in HL.
- Includes the following headings in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be **bolded** and placed at the beginning of Highlights and read as follows: “**These highlights do not include all the information needed to use [insert name of drug product in UPPER CASE] safely and effectively. See full prescribing information for [insert name of drug product in UPPER CASE].**”

- **Product Title**
 - Must be **bolded** and include the proprietary and nonproprietary drug names, followed by the drug’s dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - Must include the 4-digit year of the initial U.S. approval of the new molecular entity (NME), new biological product, or new combination of active ingredients. If this is an NME, the year corresponds to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary must not exceed a length of 20 lines.
 - Requires a heading in upper-case bolded letters, containing the word “WARNING” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If Highlights boxed warning is identical to FPI boxed warning, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions.
 - The heading and, if appropriate, subheading of each labeling section affected by the change must be listed with the date (MM/YYYY format) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed in HL for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product is a member of an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This heading must be included in HL and not omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and cross-reference to Contraindications section (4).

- **Warnings and Precautions**

- Pregnancy Category D drugs have positive human risk findings. These findings must be noted as a warning. Therefore, must state the following: “Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus.”

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” cannot be used. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include a toll free number.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA approved patient labeling or Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date will be the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading – **FULL PRESCRIBING INFORMATION: CONTENTS** – must appear at the beginning of the TOC in UPPER CASE and **bold** type.
- The headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- When a section or subsection is omitted from the FPI and TOC, the heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the summary.
- Must include a brief, concise summary of critical information and cross-reference to more detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

• Warnings and Precautions

- For Pregnancy Category D drugs, list pregnancy as a Warning and Precaution.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” cannot be used.

- For the “Clinical Trials Experience” subsection, the following verbatim statement should precede the presentation of adverse reactions:

- “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing must be separate from the listing of adverse reactions identified in clinical trials and include the following verbatim statement:

- “The following adverse reactions have been identified during post approval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JUN YAN
12/13/2010

ANN M TRENTACOSTI
12/13/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

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

Date: December 8, 2010

To: Pamela 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)

Subject: NDA: 022574
DDMAC labeling comments for Safyral (drospirenone/ethinyl
estradiol/levomefolate calcium tablets and levomefolate calcium tablets)

Background

This consult is in response to DRUP's January 14, 2010 request for DDMAC's review on the labeling materials for Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) (Safyral). DDMAC has reviewed the following labeling materials for Safyral:

Healthcare Provider Directed:

- Prescribing Information (PI)
- Carton and Container Labels (see comments below)

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 December 2, 2010. In addition, we have considered the Yasmin PI and PPI (approved April 2010) and Beyaz PI and PPI (approved September 2010) in our review of the draft Safyral labeling.

Our comments on the carton/container labeling is based on the submission found in EDR [\\CDSESUB1\EVSPROD\NDA022574\022574.ENX].

We offer the following comments:

PI & PPI

Please see our attached comments.

Carton/Container Labeling

- Safyral Sample 1s Carton
- Safyral Sample 5s Carton

- Safyral Trade 1s Carton
- Safyral Trade 3s Carton

○

(b) (4)



DDMAC has no comments on the following carton/container labels at this time:

- Safyral Day Label
- Safyral Sample Foil
- Safyral Trade Foil

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

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

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/s/

JANICE L MANIWANG
12/08/2010

CARRIE A NEWCOMER
12/08/2010

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 27, 2010

To: Scott Monroe MD, Director,
Division of Reproductive and Urology Products

Through: Melina Griffis, R.Ph, Team Leader
Denise Toyer, Pharm D, Deputy Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Safyral (Drospirenone/Ethinyl Estradiol/Levomefolate Calcium
and Levomefolate Calcium) Tablets, 3 mg/0.03 mg/0.451 mg and
0.451 mg

Application Type/Number: NDA # 22574

Applicant/sponsor: Bayer

OSE RCM #: 2010-1248

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1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Safyral (NDA 022574) submitted on June 2, 2010 for medication error potential. The proposed proprietary name, Safyral, was evaluated under separate review (OSE #2010-1236). We provide recommendations in Section 3.1 with regards to the proposed product labels and labeling.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the trade and sample foils, labels and labeling submitted December 16, 2009 to identify vulnerabilities that could lead to medication errors. (See Appendices A through D). This evaluation also compared the proposed labels and labeling for NDA 022574 to the approved labels and labeling for the product, Yasmin, which has the same active ingredients, Drospirenone and Ethinyl Estradiol, but no Levomefolate Calcium.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation finds the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We provide recommendations below that aim at reducing the risk of medication errors and request these recommendations be communicated to the Applicant prior to the approval of this NDA.

We are willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Maria Wasilik, OSE Project Manager, at 301-796-0567.

3.1 COMMENTS TO THE DIVISION

The established name should appear in parenthesis with the coinciding strengths outside of the parenthesis. This presentation of active drug and strength follows the presentation of Beyaz***, which is another folate containing oral contraceptive.

Additionally, established names are typically presented with commas between the ingredients. DMEPA notes that ONDQA has recently approved an oral contraceptive which contains similar ingredients to the product under review with slashes between the ingredients, thus DMEPA defers to ONDQA for the acceptable presentation of the established name.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.2 COMMENTS TO THE APPLICANT

A. Sample and Trade Foil Label

- 1) The presentation of the proprietary name as it appears on the sample foil is confusing as the placement of active drug names is different on each line. Patients or practitioners may assume that both the third and fourth row of tablets contain only Levomefolate Calcium as this is the only name presented next to those tablets. Condense the active ingredients so that they appear together on one line. The appearance of the proprietary name and established name on the foil should appear as follows, with the slashes representing the seven pills per week:

Safyral

Drospirenone/Ethinyl Estradiol/Levomefolate Calcium Tablets

& Levomefolate Calcium Tablets

B. Carton Labeling

- 1) The presentation of the established name and strengths as they appear with the green background is not prominent or easy to read. Using bold font will allow the established name and corresponding strengths to appear more visible.
- 2) The physician sample contains the statement "Patient Starter Pack" which is not in accordance with 64 FR 67720. A physician sample and a starter pack denote two different types of packaging, one which requires a prescription and one which is given in place of an actual prescription form. As such, a drug product which is to be given to a patient by a physician as a sample cannot use the term 'starter.'

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

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/s/

ANNE CRANDALL
08/27/2010

MELINA N GRIFFIS
08/27/2010

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 10, 2010

FROM: Hyojong Kwon, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 8/10/10*
Acting Team Leader, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-574 and NDA 22-532,
Drospirenone 3 mg, Ethinyl estradiol 0.03 mg,
Levomefolate calcium 0.451 mg Tablets, Sponsored by
Bayer HealthCare Pharmaceuticals Inc.

TO: Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products (DRUP)
Office of New Drugs

The review division (DRUP) requested that the Division of Scientific Investigations (DSI) conduct an audit of the clinical and bioanalytical portions of the following bioequivalence study.

Study Number: 309662 (A27410)

Study Title: Open-label, randomized, three-fold crossover study to investigate the bioequivalence of two different tablet formulations containing 0.03 mg ethinylestradiol (EE) and 3 mg drospirenone (DRSP) without [SH T470FA] and with [SH T04532A] 0.451 mg Metafolin®, and to investigate the bioequivalence of two different tablet formulations containing 0.451 mg Metafolin® without [SH T04532C] and with 0.03 mg EE/3 mg DRSP [SH T04532A] in 42 healthy young women

The clinical portion of Study 309662 was conducted and audited at Scope International Life Sciences AG, Hamburg, Germany (8/2-8/6/2010). Bioanalytical portion of this study was conducted and audited at (b)(4)

(b)(4) (7/26-7/30/2010). Following the inspections, a

Form FDA 483 was issued for analytical portion at (b)(4) (b)(4) (Attachment 1) but there was no significant finding at the clinical site. The EIR cover memo for the outcomes of an inspection at (b)(4) were submitted via DAARTS on 5/24/2010 in regards to NDA 22-532. The objectionable items, the (b)(4)s response (dated 8/4/2010, attachment 2) and our evaluation follow:

(b)(4);

1. Failure to demonstrate reliability at the lower limit of quantification (LLQ) for ethinylestradiol and drospirenone.

-For example,

(1) Ethinylestradiol: Some chromatograms of 2 pg/mL (LLQ) calibrators were not automatically integratable, which resulted in re-integration or rejection of LLQ calibrator (STD-A) in multiple runs: AQ17-001, AQ09-004, AQ09-006, AQ17-011, AQ17-012, AQ09-005 and AQ09-008.

(2) Drospirenone: the LLQ calibrator at 0.1 ng/mL and/or the low quality control sample (LQC) at 0.3 ng/mL were re-integrated in approximately 20 of 26 runs: e.g. runs AQ13-004, AQ13-007, AQ07-001a and AQ06-001.

The firm's identification of poor chromatography was not consistent in that many chromatograms for LLOQ calibration standards for ethinylestradiol and drospirenone and LQCs for drospirenone were not integrated automatically and re-integrated to be acceptable due to poor peak separation and/or poor signal to noise ratio for ethinylestradiol and drospirenone, respectively. During the inspection and in the firm's written response to Form FDA 483 (Attachment 2), the firm acknowledged that the assay did not demonstrate acceptable sensitivity at lower concentrations for ethinylestradiol and drospirenone. DSI made a similar observation for Study 309664 in NDA 22-532.

In light of these findings, accuracy of the data cannot be assured for ethinylestradiol concentrations below 4 pg/mL and drospirenone concentrations below 0.5 ng/mL, respectively. In the firm's response to Form FDA 483 (See Attachment 2), the firm indicated that they would incorporate tables with the required reanalysis results for analytical reasons in amendments to the bioanalytical reports for both ethinylestradiol and drospirenone. Please note that a revised clinical report (amendment) is expected to be submitted to DRUP by the sponsor.

2. Failure to establish a written procedure for re-assay due to internal standard (IS) response variation.

- Specifically, re-assay of samples due to IS response variation was not consistent. For example, when IS responses of the samples were less than 30% of the mean IS response of samples of the run, a sample (ID 1059) was re-assayed but other samples (ID 1735 and ID 0819) were not re-assayed.

The firm did not establish objective criteria for re-assay due to IS variation. There was no documentation to justify selective and inconsistent re-assay of samples due to IS variation. In the firm's response to Form FDA 483 (Attachment 2), the firm acknowledged this observation and indicated that they made corrections to reported data in the amendment submitted along with the written response (Attachment 2).

3. The quality control samples (QCs) (6, 125, 800 pg/mL) and calibration standards (2, 4, 10, 50, 200, 500, 800 and 1000 pg/mL) for ethinylestradiol used in the analytical runs were not representative of ethinylestradiol concentrations observed in study plasma samples.

- The maximum observed concentration of ethinylestradiol was 121 pg/mL

In the firm's response to Form FDA 483 (See Attachment 2), the firm acknowledged the observation and evaluated the assay performance using 5 calibrators (2, 4, 10, 50 and 200 pg/mL) and 2 QCs (6 and 125 pg/mL) representative of ethinylestradiol plasma concentrations in the bioanalytical runs. Although there were only 5 calibrators and 2 QCs in these evaluations, the results of all LQCs and MQCs were found acceptable. DSI recommends accepting the firm's evaluation.

4. Failure to evaluate appropriate validation experiments.

-For example,

- (1) matrix effect was not evaluated.
- (2) freeze/thaw (F/T) stability experiments were not conducted to reflect the condition of plasma samples collected from subjects receiving ethinylestradiol (EE), drospirenone (DRSP) and metafolin treatment. For example, two individual F/T stability experiments were conducted for EE and for DRSP without the presence of other compound.

(b)(4) separately assessed matrix variability to evaluate the effect of six different matrix lots on assay performance for each compound in pre-study method validation. In the firm's written response to Form FDA 483, the firm indicated that they would submit the results of matrix effect and F/T stability of EE and DRSP in the presence of metafolin by August 18, 2010. Another analytical site, (b)(4) conducted F/T stability experiments of metafolin in the presence of EE and DRSP and provided acceptable results, as noted in the EIR cover memo for NDA 22532 (dated 5/24/2010). In light of the acceptable results of this F/T stability in the (b)(4) report and matrix variability assessment in the validation report, DSI is of the opinion that the pending results for the new validation experiments should not delay the approvability decision of the Review Division.

Conclusion

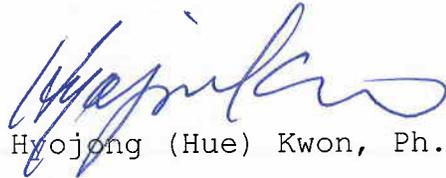
Following our evaluation of the inspectional findings and the firm's response to Form FDA 483, DSI recommends the followings:

1. The firm should recalculate subject concentrations with new calibration curves for ethinylestradiol from 4 pg/mL to 1000 pg/mL and use 4 pg/mL as LLOQ (483 Item 1). The reviewer should evaluate re-calculated ethinylestradiol concentrations using the amended report (amendment 02) that the firm planned on submitting by August 18, 2010.
2. The firm should recalculate subject concentrations with new calibration curves for drospirenone from 0.5 ng/mL to 100 ng/mL and use 0.5 ng/mL as LLOQ (483 Item 1). The reviewer should evaluate re-calculated drospirenone concentrations in the amended report (amendment 02) that the firm planned on submitting by August 18, 2010.
3. The reviewer should replace the data for the following samples with the values in the table included in the firm's written response to Form FDA 483 (483 Item 3) in bioequivalence evaluation.

Table 1 Individual ethinylestradiol results with low internal standard response				
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, -0.5 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.

Page 5 of 8- NDA 22-574 and NDA 22-532, Drospirenone 3 mg, Ethinyl estradiol 0.03 mg, Levomefolate calcium 0.451 mg Tablets

After you have reviewed this transmittal memo, please append it to the original NDA submission.

 8/10/2010
Hyojong (Hue) Kwon, Ph.D.

DSI Final Classification:

VAI - 

(b) (4)

NAI - Scope International Life Sciences AG, Hamburg, Germany

CC:

CDER DSI PM TRACK

HFD-48/Kwon/Rivera-Lopez/Ball/Haidar/CF

OND/DRUP/Pamela Lucarelli/Doanh Tran (HFD-580)

Draft: HK 8/8/2010

Edit: MFS 8/10/2010, MYK 8/10/2010

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

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/s/

HYOJONG KWON

08/10/2010

Appendix in the firm's written response will be sent via email to PM due to large size of the file. Dr. Yau signed the hard copy on 8/10/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022574 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: dropirenone/ethinyl estradiol/levomefolate calcium Dosage Form: tablets Strengths: dropirenone 3 mg/ethinyl estradiol 0.03 mg/levomefolate calcium 0.451 mg		
Applicant: Bayer HealthCare Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: November 16, 2009 Date of Receipt: November 16, 2009 Date clock started after UN:		
PDUFA Goal Date: September 16, 2009	Action Goal Date (if different):	
Filing Date: December 31, 2009	Date of Filing Meeting: December 23, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1, 4		
Proposed indication(s)/Proposed change(s) (b) (4) <div style="background-color: #cccccc; height: 15px; width: 100%;"></div>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 072287				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?		X		Refer to NDA 022532
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?		X		Refer to NDA 022532
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			Refer to NDA 022532
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>		X		
REMS consulted to OSE/DRISK?		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		Applicant plans to submit trade name request
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 6, 2009 Guidance Meeting on August 4, 2005 Guidance Meeting on January 6, 2006	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 23, 2009

BLA/NDA/Supp #: NDA 022574

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: dropirenone/ethinyl estradiol/levomefolate calcium

DOSAGE FORM/STRENGTH: dropirenone 3 mg/ethinyl estradiol 0.03 mg/levomefolate calcium 0.451 mg

APPLICANT: Bayer HealthCare Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (b) (4)

BACKGROUND: Dropirenone/ethinyl estradiol/levomefolate calcium is developed for the primary indication of improvement in folate status in women who elect to use an oral contraception. Dropirenone/ethinyl estradiol/levomefolate calcium will contain 21 tablets of drospirenone 3mg, ethinyl estradiol 0.03 mg and 0.451 mg of Metfolin and (b) (4) tablets of 0.451 mg of Metfolin. This product is a New Molecular Entity (NME).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pam Lucarelli	Y
	CPMS/TL:	Jennifer Mercier	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Daniel Davis	Y
	TL:	Lisa Soule	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		

	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Doanh Tran	Y
	TL:	Myong-Jin Kim	N
Biostatistics	Reviewer:	Sonia Castillo Kate Dwyer (covering)	N Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Leslie McKinney	
	TL:	Alex Jordan	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	N
	TL:	Moo-Jhong Rhee Donna Christner - PAL	N Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Project Manager:	Maria Wasilik	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer: Roy Blay	N
	TL:	
Other reviewers	Scott Monroe (DRUP)	Y
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: Refer to NDA 022532</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
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REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, Office Director	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

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

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/s/

PAMELA LUCARELLI
01/05/2010

JENNIFER L MERCIER
01/05/2010