CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022532Orig1s000

OTHER REVIEW(S)

SEALD LABELING REVIEW

This review identifies 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 022532
APPLICANT	Bayer Healthcare Pharmaceuticals, Inc.
DRUG NAME	Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
SUBMISSION DATE	August 24, 2009
PDUFA DATE	September 24, 2010
SEALD REVIEW DATE	September 21, 2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), "none" is stated. If clearly inapplicable sections are omitted from the FPI, "not applicable" is stated. In addition, "not applicable" is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

Highlights (HL):

- **Highlights Limitation Statement:** None.
- **Product Title Line:** None.
- **Initial U.S. Approval:** None.
- **Boxed Warning:** None.
- **Recent Major Changes:** N/A.
- **Indications and Usage:** None.
- **Dosage and Administration:** None.
- **Dosage Forms and Strengths:** None.
- **Contraindications:** None.
- **Warnings and Precautions:** None.

- **Adverse Reactions:** Add "(6.1)" to both bullets in order to reference the corresponding section in the FPI.
- **Drug Interactions:** None.
- **Use in Specific Populations:** None.
- **Patient Counseling Information Statement:** None.
- **Revision Date:** None.

Table of Contents (TOC):

None.

Full Prescribing Information:

Boxed Warning: N/A.

1 Indications and Usage: None.

2 Dosage and Administration: None.

3 Dosage Forms and Strengths: None.

4 Contraindications: None.

5 Warnings and Precautions: None.

6 Adverse Reactions: None.

7 Drug Interactions: None.

8 Use in Specific Populations: None.

9 Drug Abuse and Dependence: N/A.

10 Overdosage: None.

11 Description: None.

12 Clinical Pharmacology:. Subsection 12.3: Correct the table number to "Table 1." Remove bolding in the table to be consistent with Table 2 in Section 14.2.

13 Nonclinical Toxicology: None.

14 Clinical Studies: Subsection 14.2: Correct the table number to “Table 2.”

15 References: N/A.

16 How Supplied/Storage and Handling: None.

17 Patient Counseling Information: None.

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/s/

JUN YAN
09/21/2010

LAURIE B BURKE
09/22/2010

MEMORANDUM

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

DATE: June 30, 2010

TO: Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products
(HFD-580)

FROM: Sean Y. Kassim, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Michael F Kelly for MKY 6/30/10
Acting Team Leader, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Second addendum to the Review of EIR Covering NDA 22-532, Drospirenone/Ethinylestradiol/Levomefolate Calcium, 3 mg/0.02 mg/0.451 mg, Sponsored by Bayer Healthcare Pharmaceuticals, Inc.

At the request of the Division of Reproductive and Urologic Products (DRUP), the Division of Scientific Investigations (DSI) audited studies 309664, 309763, and 310662 associated with NDA 22-532. On 3/1/2010, DSI forwarded recommendations to DRUP for the inspection of Study 309664 at (b) (4) 1/18-22/10), involving measurements of ethinyl estradiol (EE) and drospirenone (DRSP). On 5/24/10 DSI forwarded recommendations to DRUP for the remaining studies. On 6/17/10 DSI received a third response to the Form FDA 483 observations. This current review evaluates the third response, concerning the analytical portions of Study 309763 and Study 310662:

Study 309763*: "A Randomized, Double-Blind, Double-Dummy, 2 Parallel Arms Clinical Trial to Assess the Pharmacodynamic Effect on Plasma Folate and Red Blood Cell Folate and to Compare the Profile of Circulating Folate Metabolites during 24 Weeks of Treatment with an Oral Contraceptive containing Ethinylestradiol, Drospirenone, and L-5-Methyltetrahydrofolate (SHT04532A and SH T04532C) or Yasmin (SH T04532D and SH T04532PC) Co-administered with Folic Acid (SH K04532B) Followed

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* This study is also referred to in the application and at the sites as, A39814; A34009 and A34010; and (b) (4) V7227 and (b) (4) V7430/02.

by 20 Weeks of Open-Label Treatment with Yasmin only (Folate Elimination Phase) in Women Seeking Contraception"

Study 310662[†]: "Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Study to Investigate Plasma Folate, Red Blood Cell Folate and Homocysteine Levels during a 24-Week Oral Administration of an Oral Contraceptive (OC) containing Folate Compared to OC Alone"

Analytical Site for Studies 309763, 310662:

(b) (4)

Following the inspection of the analytical site (3/1-5/10), Form FDA-483 was issued. DSI reviewed the firm's first two responses in the earlier addendum (5/24/10). DSI received the firm's third response to the inspectional findings dated 6/9/10 (Attachment 1). The third response pertains to the first three observations from the Form FDA-483. DSI's evaluation of the third response for the inspection of studies 309763 ((b) (4) V7227 and (b) (4) V7430/02) and 310662 ((b) (4) V7523 and V8098) follow:

Pertaining to the microbiological folate assay used for (b) (4) V7227, V7523, and V8098:

1. **Failure to perform sufficient stability analyses. Long-term stability was only completed for 10-months. Study sample analysis spanned 19 (309763) and 22 (310662) months. Also, freeze/thaw stability was only performed with previously frozen RBC and plasma.**

DSI's previous evaluation of this observation indicated that the firm did not have sufficient frozen stability data as the High- and Medium-concentrations of quality control samples (QCs) used during analyses of whole blood samples, were prepared in phosphate-buffered saline with bovine serum albumin (PBS-BSA). Moreover, the assay results for these QC samples were outside the study sample acceptance criterion of ±15% from nominal. The third response does not address this deficiency.

(b) (4) provided additional data regarding samples prepared by king twelve never-frozen whole blood samples with 200 ng/mL folate, and twelve never-frozen plasma samples with 8 ng/mL

[†] This study is also ferred to in he application and at the sites as, A43598; A36931; and (b) (4) V7523 and (b) (4) V8098.

folate. Ten of twelve samples (>83%), for both blood and plasma, recovered more than 85% of the added folate after a single freeze-thaw cycle. This portion of the response is satisfactory.

2. Failure to use appropriate calibrators and quality controls. Folate concentrations were determined in human whole blood and human plasma study samples using calibrators and QCs prepared in buffer (PBS BSA). Validation experiments were only evaluated at one level in whole blood (endogenous + 200 ng/mL folate) and one level in plasma (endogenous + 8 ng/mL folate).

(b) (4) evaluated folate concentrations in whole blood samples ked at 100, 200, and 300 ng/mL more than endogenous (66 to 168 ng/mL, average 113 ng/mL in six subjects), and in plasma samples spiked at 3, 8, and 12 ng/mL more than endogenous (4.4 to 11.4 ng/mL, average 7 ng/mL in six subjects). The assays recovered 85-115% of the added folate in more than 66% of assays, except the 3 ng/mL folate spiked into plasma. Less than 66% of the 3 ng/mL folate spiked samples were measured within 85-115% of the expected 3ng/mL spike (7 of 12 samples from six subjects), however using the 80-120% acceptance criterion, 8 of the 12 samples (66%) are acceptable. DSI concludes that the accuracy of the g/mL folate spike in plasma cannot be assured. Note: (b) (4) used the 85-115% recovery specification during the studi

3. Failure to determine sufficient dilution linearity. Six samples required 8X dilution while only 5X dilution linearity was established.

The third response evaluated recovery of folate added to samples and diluted 8-fold for assay. Only six of twelve diluted blood samples and only six of eleven diluted plasma samples recovered 85-115% of the expected concentrations. Therefore, the validation has only confirmed 5-fold dilutions as accurate.

NOTE: The response includes data from an earlier experiment that were discarded due to inconsistent results. Normally all these data would be evaluated, however, the firm explained (Attachment 2) that the excluded experiment was performed differently from the previous studies. The data evaluated in the response used conditions closely resembling those of the studies.

Conclusions:

Following the above inspections, and a review of (b) (4) responses, DSI concludes that:

For studies 309763 and 310662 (Folate by Microbiologic Method):

A. Adequate long-term frozen stability has not been established at the high (400 ng/mL) and medium (200 ng/mL) concentrations encountered during whole blood analysis. This recommendation is unchanged from our original memorandum.

B. (b) (4) has now demonstrated sufficient stability of folate added in freshly-collected blood and plasma, and measured after a single cycle of freezing-thawing.

C. (b) (4) has demonstrated sufficient accuracy for assays of folate in plasma and whole blood, except for folate determinations of 3 ng/mL spiked into plasma. If the ±15% acceptance criterion is used, DSI recommends that plasma folate results below 3 ng/mL should be omitted from analysis.

D. The accuracy of folate assays after 8-fold dilution has not been demonstrated. DSI continues to recommend that blood and plasma folate results from six samples diluted 8-fold should be omitted.

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

6-30-10

Sean Y. Kassim, Ph.D.

Final Classifications:

VAI - (b) (4)

FEI: (b) (4)

cc:
DSI/GLPBB/Ball/Haidar/Kassim/Kwon/Yau/Rivera-Lopez/CF
OND/DRUP/Monroe/Lucarelli
Draft: SYK 6/24/10, 6/29/10
Edit: MFS 6/25/10, 6/29/10
DSI: 6023; O:\Bioequiv\EIRCover\22532bay.yaz.addendum.doc
FACTS: 1137796

Email:
Diane.VanLeeuwen@fda.hhs.gov
CDER DSI PM TRACK

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:	May 6, 2010
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Drug Products
Through:	Melina Griffis, RPh, Team Leader Denise Toyer, Pharm D, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Beyaz (Drospirenone, Ethinyl Estradiol, and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets) 3 mg/0.02 mg/0.451 mg and 0.451 mg
Application Type/Number:	NDA 022532
Applicant/sponsor:	Bayer Healthcare Pharmaceuticals
OSE RCM #:	2009-1841

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Beyaz (NDA 022532) submitted on December 16, 2009. The proposed proprietary name, Beyaz, was evaluated under separate review (OSE # 2009-2462). We provide recommendations in Section 3.1 with regards to the proposed product labels and labeling.

2 METHODS AND MATERIALS REVIEWED

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.) This evaluation also compared the proposed labels and labeling for NDA 022532 to the approved labels and labeling for YAZ.

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, project manager, at 301-796-0567.

3.1 COMMENTS TO THE DIVISION

A. General Comments

1. The established name as presented suggests this combination oral contraceptive provides all three active ingredients in all tablets which is misleading. However, this product includes 24 tablets which all contain the three active ingredients and the remaining four tablets which only contain Levomefolate Calcium. DMEPA recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC) and Hitesh Shroff, the assigned Office of New Drug Quality Assessment (ONDQA) Chemist, regarding the appropriate expression of the established name of this product. We offer the following recommendation for consideration:

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

Drosperinone, Ethinyl Estradiol, and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets

3 mg/0.02 mg/0.451 mg and 0.451 mg

3.2 COMMENTS TO THE APPLICANT

A. General Comments

1. (b) (4)

2. Revise the presentation of the established name on the carton labeling and day label sheet so that it shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).

3. Increase the prominence of the strength on the carton labeling and day label sheet to be commensurate with the established name.

B. Sample and Trade foils

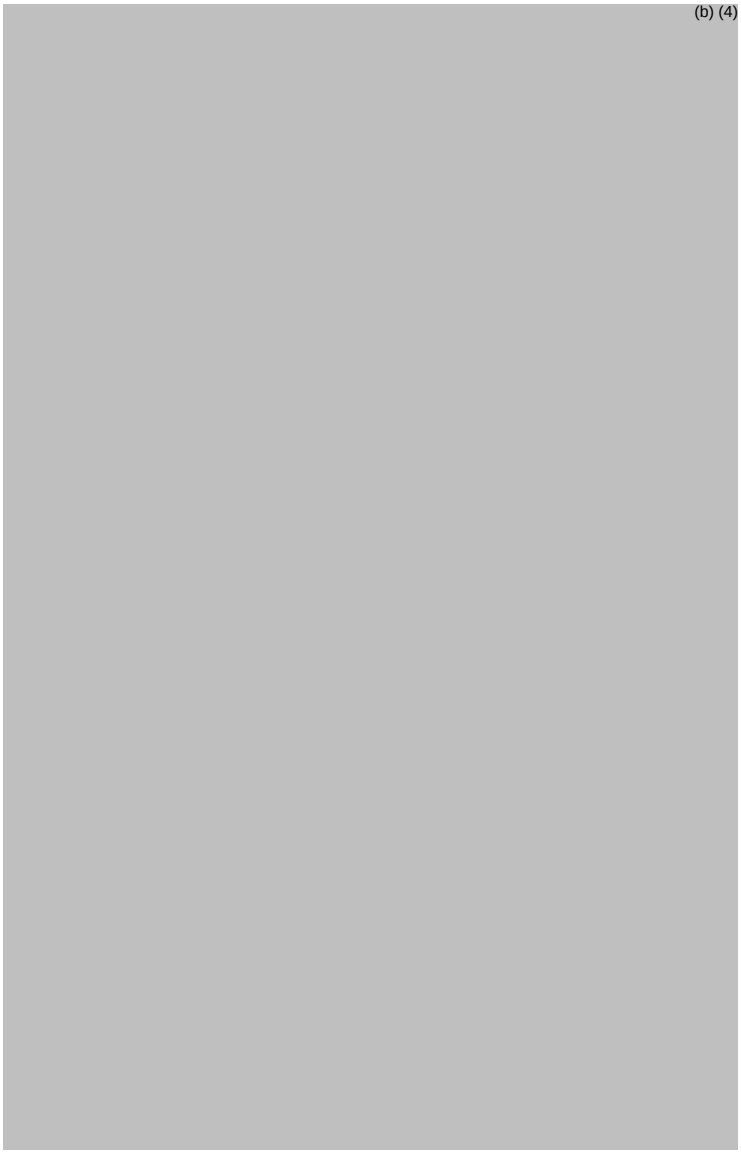
1. (b) (4) Revise the presentation of the proprietary and established names on the foils so the proprietary name and the entire established name appear together (either on the front or back) as well as in a format providing for the legibility of the proprietary and established names before and after the tablets have been remove from the foil.

APPENDICES

Appendix A: Sample and Trade foils (front and back)

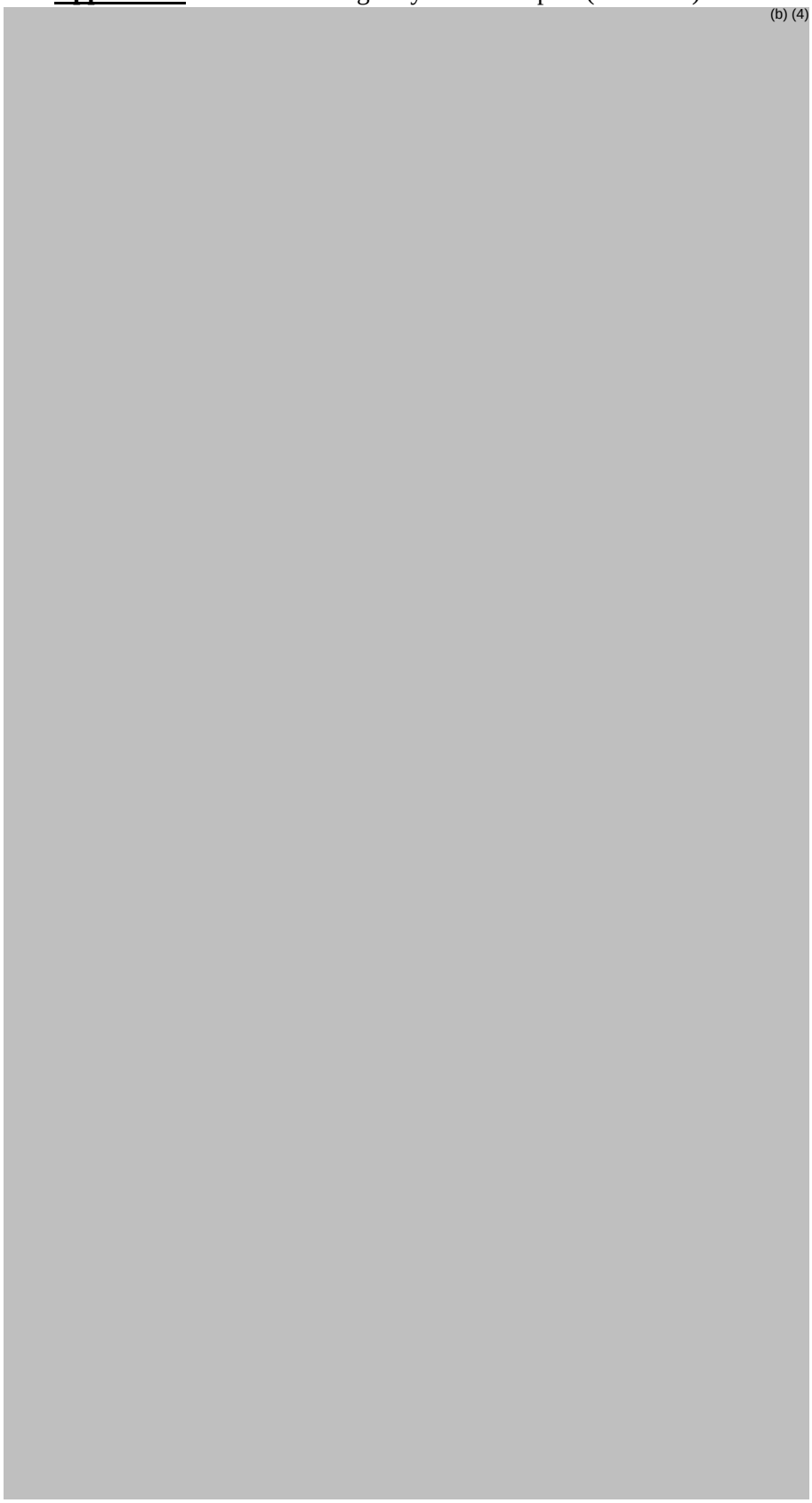
Appendix C: Carton Labeling (28 tablets – one unit)

Appendix D: Carton Labeling Patient Starter Pack (physician sample - One unit)



Appendix E: Carton Labeling (28 tablets - three units)

Appendix F: Carton Labeling Physician Samples (five units)



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

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/s/

RICHARD A ABATE
05/06/2010

MELINA N GRIFFIS
05/06/2010

DENISE P TOYER
05/06/2010

CAROL A HOLQUIST
05/06/2010

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: March 15, 2010

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

THROUGH: Dan Davis, M.D., Clinical Reviewer
Lisa Soule, M.D., Clinical Team Leader
Division of Reproductive and Urologic Products

FROM: Pamela Lucarelli, Regulatory Health Project Manager
Division of Reproductive and Urologic Products

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 022532
Beyaz (drospirenone 3 mg, ethinyl estradiol 0.02 mg, levomefolate calcium 0.451 mg)

Study/Site Identification:

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)
A43598 (Protocol 310662)	Site # 108 William D. Koltun, MD Medical Center for Clinical Research 9040 Friars Road, Suite 540 San Diego, CA 92108	N/A

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **May 1, 2010.** We intend to issue an action letter on this application by **June 24, 2010**.

Should you require any additional information, please contact Pamela Lucarelli, Regulatory Health

Project Manager at (301) 796-3961.

Concurrence:

Dan Davis M.D. _____Medical Reviewer
Lisa Soule M.D._____Medical Team Leader

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

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/s/

PAMELA LUCARELLI
03/15/2010

LISA M SOULE
03/15/2010

MEMORANDUM

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

DATE: March 1, 2010

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

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 3/1/2010
Acting Team Leader, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-532, Drospirenone/Ethinylestradiol/Levomefolate Calcium, 3 mg/0.02 mg/0.451 mg, (b) (4)

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: 309664

Study Title: Open-label, randomized, three-fold crossover study to investigate the bioequivalence of two different tablet formulations containing 0.02 mg ethinylestradiol (EE) and 3 mg drospirenone (DRSP) without [SH T00186D] and with [SH T04532B] 0.451 mg L-mefolinate (Metafolin),and to investigate the bioequivalence of two different tablet formulations containing 0.451 mg L-mefolinate (Metafolin) without [SH T04532C] and with 0.02 mg EE/3 mg DRSP [SH T04532B] in 42 healthy young women

Inspection of the clinical portion of Study 309664 is tentatively scheduled in the 2nd week of March, 2010 at Dinox, Groningen, The Netherlands. Bioanalytical portion of this study was inspected at (b) (4) (b) (4) Following the inspection

of [redacted] (b) (4), Form 483 was issued (Attachment 1). The objectionable items, the [redacted] (b) (4) response (dated 2/16/2010, Attachment 2) and our evaluation follow:

[redacted] (b) (4)

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

-For example,
(1) Ethinylestradiol: The chromatograms at 2 pg/mL were not integratable and rejected in multiple runs: AQ09-001, AQ09-003, AQ17-005, AQ17-006, AQ17-008 and AQ17-009.
(2) Drospirenone: the LLOQ calibration standard at 0.1 ng/mL and the low quality control sample (LQC) at 0.3 ng/mL were re-integrated in approximately 18 of 21 runs: e.g. runs AQ06-001, AQ06-002, AQ07-001and AQ14-001.

The firm's identification of poor chromatography was not consistent in that many LLOQ calibration standards for ethinylestradiol and drospirenone and LQC of dospirenone were not integrated automatically and re-integrated to be acceptable due to poor separation and/or poor signal to noise ratio for ethinylestradiol and drospirenone, respectively. During the inspection and in the firm's response to Form 483 (See Attachment 2), the firm also acknowledged that the assay did not demonstrate acceptable sensitivity at lower concentrations for ethinylestradiol and drospirenone.

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.

2. Failure to document the justification and establish objective criteria for modifying the chromatographic integration parameters for ethinylestradiol and drospirenone in multiple runs.

- For example, the acquisition software audit trail showed modification of integration parameters for certain samples during the analytical run but without documenting the justifications.

(1)Ethinylestradiol:
(a) STD-C (10 pg/mL) and Samples 0868, 0871, 0911, 0915 were modified in run AQ17-010.

(b) STD-D (50 pg/mL) and Samples 1271, 1314, 13211338 were modified in run AQ09-004.
(2)Drospirenone:
(a) STD-A, -B, -C and QC-A1, QC-A2 and Samples 1355, 1356, 1357, 1377, 1378, 1379, 1380, 1401, 1420 were modified in run AQ06-009.
(b) STD-B, -C, -D and and QC-A1, QC-A2 and Samples 0742, 0750, 0756, 0758, 0780, 0802, 0803, 0804, 0822, 0823, 0824, 0825 were modified in run AQ06-003.

The firm did not establish objective criteria for modifying the chromatographic integration parameters. There was no documentation to justify selective re-integrations of calibration standards and QC samples using different integration parameters from original parameters used to automatically integrate the rest of samples in the same run. During the inspection, DSI found that the original integration parameters used in automatic integration failed to produce consistent integration or peak separations between the analyte and baseline noise at low concentrations. In the firm's response to Form 483 (See Attachment 2), the firm acknowledged this observation and indicated that they would implement improved re-integration procedure.

3. Failure to reject an analytical run when calibration standards failed the acceptance criteria.

-For example, although > 1/3 of calibration standards in run AQ07-003 failed to meet the acceptance criteria, instead of rejecting the run, the run was calculated with a replacement set of calibration standards from run AQ07-004, under SOP P8.2.3.

According to the firm's bioanalytical procedure SOP P8.2.3, the firm did not reject this run when > 1/3 of calibration standards in run AQ07-003 failed to meet the acceptance criteria. Instead, the firm performed regression analysis of this run with replacement calibrators from run AQ07-004 and accepted run AQ07-003. This procedure is not justified or adequate in that the replacement set of calibration standards were not processed with study samples and thus cannot be considered representative of the study samples. In the firm's response to Form 483 (See Attachment 2), the firm stated that they decided to reject run AQ07-003. The firm further stated that the summary statistics as well as the results table would be processed without the results from run AQ07-003 and these new summary statistics and results table would be incorporated in an amendment to the bioanalytical report by March 22, 2010.

4. Failure to process calibration standards with QCs and study samples for run AQ06-008.

- After a suspected processing error in preparing one of the original calibrators, a replacement set of calibration standards was substituted.

During the inspection, DSI found that calibration standards were not processed with QCs due to processing error in one calibrator sample and study samples for run AQ06-008 and a replacement set of calibration standards were used to calculate concentrations of study samples and QCs. Instead of replacing only the calibration standards, the firm should have processed a new set of calibration standards and QCs with study samples to assure accuracy of the data. In the firm's response to Form 483 (See Attachment 2), the firm acknowledged this 483 observation and indicated that they would correct the study procedure to no longer allow the preparation of a new calibration curve separate from quality control samples and study samples.

5. Failure to reject run AQ14-003 after observing chromatographic interference with drospirenone in calibration standard (STD) A. The same blank matrix (ID 5038) was used to prepare all calibrators and QCs for this run.

Blank matrix (ID 5038) was used to prepare calibrators and QCs for drospirenone on September 24, 2007 for all runs analyzed from September 25, 2007 till October 25, 2007 (See Table below). The firm rejected STD A when chromatographic interference was observed in blank matrix (ID 5038). In the firm's response to Form 483 (See Attachment 2), the firm agreed with this 483 observation in that they observed interference exceeding 20% of the response of STD A and B. Then, the firm decided to reject run AQ14-003 and provided the summary statistics without the result of AQ14-003.
However, the firm did not evaluate interference of the response of calibrators/QCs prepared with the same matrix (ID 5038) in other runs.

Run ID	Date (ddmmyy)	Subject Number	Period	Sample	Run Accepted
AQ14-001	26Sep07	20,102	1, 3	1 - 20	yes
AQ14-002	28Sep07	28	1, 3	1 - 20	yes
		29	2	1 - 13, 15 - 20	
			3	1 - 20	
AQ14-003	28Sep07	101	2	1 - 20	yes
			3	1 - 14, 16 - 20	
		30	1	1 - 20	
			3	1 - 18, 20	
AQ14-004	01Oct07	33	1, 3	1 - 20	yes
		34	2, 3	1 - 20	
AQ14-005	02Oct07	35	1, 2	1 - 20	yes
		36	1	2 - 20	
			2	1 - 20	
		37	2, 3	1 - 20	
AQ14-006	03Oct07	30	1	1, 20	no
			3	1	
		39	2, 3	1 - 20	
		40	1, 2	1 - 20	
		101	2	1, 20	
AQ14-007	05Oct07	11	2	1 - 20	yes
			3	1 - 13, 15 - 20	
		32	2	1 - 12, 14, 15, 17 - 20	
		38	1, 3	1 - 20	
AQ14-008	06Oct07	41	1, 3	1 - 20	yes
		42	1, 2	1 - 20	
AQ14-009	08Oct07	27	2	11, 12	yes
		30	1	1, 20	
			3	1	
		39	2, 3	1 - 20	
		40	1, 2	1 - 20	
		42	1	9	
		101	2	1, 20	
			3	1	
AQ06-011	25Oct07	8	1	14	yes
		31	1	2 - 6	
		34	2	2 - 5	

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

- The maximum observed concentration of ethinylestradiol was 75.9 pg/mL.

In the firm's response to Form 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.

7. Failure to evaluate the long-term stability of drospirenone in plasma at -20 °C for the storage duration of the study.

- Frozen stability of drospirenone in plasma was evaluated for 115 days and 200 days, however the maximum time from sample collection to sample analysis was 251 days.

In the firm's response to Form 483 (See Attachment 2), the firm acknowledged the observation and decided to reject the data of all 120 samples that had been stored longer than 200 days. The firm indicated in their response that a bioanalytical report will be amended to reflect the rejection of these 120 results by March 22, 2010.

8. Failure to report all samples that underwent repeat analysis in the analytical reports.

- The result tables, "Suspected values: Original, repeat and reported concentrations" for ethinylestradiol and drospirenone do not include samples repeated for analytical reasons.

In the firm's response to Form 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.

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 establish new calibration curves for ethinylestradiol from 4 pg/mL to 1000 pg/mL and re-calculate all subject concentrations using the new calibration curves with 4 pg/mL as LLOQ (See 483 Item 1). The reviewer should evaluate re-calculated ethinylestradiol concentrations using the new calibration curves and exclude any concentration below 4 pg/mL for bioequivalence assessment.
2. The firm should establish new calibration curves for drospirenone from 0.5 ng/mL to 100 ng/mL and re-calculate all subject concentrations using the new calibration curve

with 0.5 ng/mL as LLOQ. The reviewer should evaluate drospirenone concentrations using the new calibration curves and exclude any concentration below 0.5 ng/mL for bioequivalence assessment. (See 483 Item 1).

3. The reviewer should exclude data for drospirenone from run AQ007-03 (Subjects 5 and 6 (Period 2 and 3)) (See 483 Item 3) and AQ06-008 (Subject 27 (Period 1 and 2) and Subject 31 (Period 1 and 3)) (See 483 Item 4) in bioequivalence evaluation.
4. The firm should evaluate the interference of blank reagent and matrix sample as well as the interference of the response of STD A and B prepared with the same matrix (ID 5038) in all runs post September 24, 2007. If the observed interference was more than 20% of the response of STD A and B in any run, the firm should reject this run as in the firm's response (dated 2/16/2010) and provide reanalysis of the result in their amendment (See 483 Item 5).
5. The reviewer should exclude data for drospirenone in the samples analyzed outside of 200-days long term frozen stability established in the validation experiment (See 483 Item 7).

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

Hyojong (Hue) Kwon, Ph.D.

DSI Final Classification:
VAI - (b) (4)

cc:
CDER DSI PM TRACK
HFD-48/Kwon/Rivera-Lopez/CF
OND/DRUP/Pamela Lucarelli (HFD-580)
Draft: HK 2/19/2010
Edit: JAK 2/22/2010, MYK 3/1/2010
File:6009 O:\BE\EIRCOVER\22532 sch dros-eth.doc
FACTS 1118001

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

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

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/s/

HYOJONG KWON
03/02/2010
Dr. Yau signed the hard copy on 3/1/2010.

DSI CONSULT: Request for Clinical Inspections

Date: December 11, 2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Roy Blay, Ph.D., Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Dan Davis, M.D., Clinical Reviewer
Lisa Soule, M.D., Clinical Team Leader
Division of Reproductive and Urologic Products

From: Pam Lucarelli, Regulatory Health Project Manager
Division of Reproductive and Urologic Products

Subject: **Request for Clinical Site Inspections**
NDA 022532 YAZ Folate (drospirenone/ethinyl estradiol and levomefolate calcium)

I. General Information

Application#:	NDA 022532
Applicant:	Bayer HealthCare Pharmaceuticals, Inc. P.O. Box 1000 Montville, NJ 07045
Contact:	Kavita Johal, Pharm.D – Assistant Director, Global Regulatory Affairs
Phone:	(973) 487-2078
E-mail:	kavita.johal@bayer.com
Drug Proprietary Name:	(b) (4) ((drospirenone/ethinyl estradiol and levomefolate calcium)
NME:	Yes (levomefolate calcium)
Review Priority:	Standard

Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): (b) (4) in women who choose to use an oral contraceptive as their method of contraception

PDUFA: June 24, 2010
Action Goal Date: June 24, 2010
Inspection Summary Goal Date: April 24, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 108 William D. Koltun, MD Medical Center for Clinical Research 9040 Friars Road, Suite 540 San Diego, CA 92108	310662 (Study A43598)	Enrolled 120 Subjects	Improvement of Folate status
Site # 103 Lori Lester Lyles, M.D. Costal Carolina Research Center 1156 Bowman Road, Suite 102 Mt. Pleasant, SC 29464	310662 (Study A43598)	Enrolled 79 Subjects	Improvement of Folate status

III. Site Selection/Rationale

We are requesting a DSI Consult for Site # 108 which enrolled 31% of the subjects and Site #103 which enrolled 21% of subjects in Study A43598.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- X Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- X Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

Should you require any additional information, please contact Pam Lucarelli, Regulatory Health Project Manager at 301-796-3961 or Dr. Dan Davis, Medical Officer at 301-796-0880.

Concurrence: (as needed)

Dan Davis M.D. _____ Medical Reviewer
Lisa Soule M.D._____ Medical Team Leader

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

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/s/

PAMELA LUCARELLI
12/11/2009

LISA M SOULE
12/11/2009

DSI CONSULT: Request for Clinical Inspections

Date: December 9, 2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Roy Blay, Ph.D., Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Dan Davis, M.D., Clinical Reviewer
Lisa Soule, M.D., Clinical Team Leader
Division of Reproductive and Urologic Products

From: Pam Lucarelli, Regulatory Health Project Manager
Division of Reproductive and Urologic Products

Subject: **Request for Clinical Site Inspections**
NDA 022532 (b) (4) (drospirenone/ethinyl estradiol and levomefolate calcium)

I. General Information

Application#:	NDA 022532
Applicant:	Bayer HealthCare Pharmaceuticals, Inc. P.O. Box 1000 Montville, NJ 07045
Contact:	Kavita Johal, Pharm.D – Assistant Director, Global Regulatory Affairs
Phone:	(973) 487-2078
E-mail:	kavita.johal@bayer.com
Drug Proprietary Name:	(b) (4) ((drospirenone/ethinyl estradiol and levomefolate calcium)
NME:	Yes (levomefolate calcium)
Review Priority:	Standard
Study Population includes < 17 years of age:	No
Is this for Pediatric Exclusivity:	No

Proposed New Indication(s): (b) (4) in women who choose to use an oral contraceptive as their method of contraception

PDUFA: June 24, 2010
Action Goal Date: June 24, 2010
Inspection Summary Goal Date: April 24, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 103 Lori Lester Lyles, M.D. Costal Carolina Research Center 1156 Bowman Road, Suite 102 Mt. Pleasant, SC 29464	310662 (Study A43598)	Enrolled 79 Subjects	Improvement of Folate status

III. Site Selection/Rationale

We are requesting a DSI Consult for Site # 103 which enrolled 21% of the subjects in Study A43598.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- X Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- X Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

Should you require any additional information, please contact Pam Lucarelli, Regulatory Health Project Manager at 301-796-3961 or Dr. Dan Davis, Medical Officer at 301-796-0880.

Concurrence: (as needed)

Dan Davis M.D. _____ Medical Reviewer
Lisa Soule M.D._____ Medical Team Leader

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

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/s/

PAMELA LUCARELLI
12/09/2009

LISA M SOULE
12/09/2009

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: December 9, 2009

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

THROUGH: Scott Monroe, M.D.
Director, Division of Reproductive and Urologic Products

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

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 022532
(b) (4)
(drospirenone 3 mg, ethinyl estradiol 0.02 mg, levomefolate calcium 0.451 mg)

Study/Site Identification:

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)
A43598 (Protocol 310662) and Study A39814 (Protocol 309763)	**Principal Investigator:** Site # 103 Lori Lester Lyles, M.D. Costal Carolina Research Center 1156 Bowman Road, Suite 102 Mt. Pleasant, SC 29464	(b) (4)

International Inspections:

We have requested an international inspection because:

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

X Other (please explain): This central lab conducted analyses of the surrogate laboratory endpoints for the two studies indicated, plasma and red blood cell folate levels.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **March 1, 2009.** We intend to issue an action letter on this application by **June 24, 2009**.

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

Concurrence:

Dan Davis M.D. _____Medical Reviewer
Lisa Soule M.D._____Medical Team Leader
Scott Monroe M.D._____Division Director

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

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/s/

PAMELA LUCARELLI
12/09/2009

LISA M SOULE
12/09/2009

SCOTT E MONROE
12/09/2009

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: October 21, 2009

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 22-532
(b) (4)
(drospirenone 3 mg, ethinyl estradiol 0.02 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)
309664[1]	**Principal Investigator:** Dr. Christine Klipping Dinox BV Hanzeplein 1, Entrance 53 9713 GZ Groningen The Netherlands Telephone: +31-50-3117057 (b) (4)	(b) (4)

[1] Open-label, randomized, three-fold crossover study to investigate the bioequivalence of two different tablet formulations containing 0.02 mg ethinylestradiol (EE) and 3 mg drospirenone (DRSP) without [SH T00186D] and with [SH T04532B] 0.451 mg L-mefolinate (Metafolin), and to investigate the

bioequivalence of two different tablet formulations containing 0.451 mg L-mefolinate (Metafolin) without [SH T04532C] and with 0.02 mg EE/ 3 mg DRSP [SH T04532B] in 42 healthy young women (study protocol number 309664, study report number A28575).

International Inspections:

We have requested an international inspection because:

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

X 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 **March 1, 2009.** We intend to issue an action letter on this application by **June 24, 2009**.

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-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

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/s/

PAMELA LUCARELLI
10/21/2009

EDWARD D BASHAW
10/21/2009

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 # 22-532 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: dropirenone/ethinyl estradiol/levomefolate calcium Dosage Form: Tablets Strengths: dropirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451 mg		
Applicant: Bayer HealthCare Agent for Applicant (if applicable):		
Date of Application: August 21, 2009 Date of Receipt: August 24, 2009 Date clock started after UN:		
PDUFA Goal Date: June 24, 2010	Action Goal Date (if different):	
Filing Date: October 8, 2009	Date of Filing Meeting: September 30, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1,4		
Proposed indication(s)/Proposed change(s): Improvement in folate status in women who elect to use an oral contraceptive		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***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.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): 72,287				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		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			

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☐ Not in arrears ☐ In arrears
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).*	

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?			X	
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)).			X	
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))? ***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).*			X	
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:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		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)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
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 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ 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? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
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? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***				

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***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.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
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? ***If no, request in 74-day letter***				
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) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***				

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

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
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) ***If yes, specify consult(s) and date(s) sent:***		X		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
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 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 30, 2009

BLA/NDA/Supp #: NDA 22-532

PROPRIETARY NAME: (b) (4)

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

DOSAGE FORM/STRENGTH: dropirenone 3 mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451 mg

APPLICANT: Bayer HealthCare Pharmaceuticals

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

BACKGROUND: YAZ Folate is developed for the primary indication of improvement in folate status in women who elect to use an oral contraception. YAZ Folate will contain 24 tablets of drospirenone 3mg, ethinyl estradiol 0.02 mg and 0.451 mg of Metfolin and four 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	Y
Cross-Discipline Team Leader (CDTL)	Lisa Soule		Y
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 (*for antimicrobial*	Reviewer:		

products)			
	TL:		

Clinical Pharmacology	Reviewer:	Doanh Tran	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Sonia Castillo	
	TL:	Mahboob Sobhan	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Leslie McKinney	Y
	TL:	Alex Jordan	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Moo-Jhong Rhee Donna Christner - PAL	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE	Project Manager:	Maria Wasilik	Y
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:		

Other attendees	Scott Monroe (DRUP)	Y
Other attendees	Pravin Jadhav (OCP)	Y
Other attendees	Li Zhang (OCP)	Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO At this time the Clinical reviewers have not determined if study site inspections are needed.
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,***	☐ YES Date if known: ☐ NO ☒ To be determined Reason:

mitigation, treatment or prevention of a disease	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, Office Director **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	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.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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)
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

/s/

PAMELA LUCARELLI
10/07/2009

JENNIFER L MERCIER
10/07/2009