

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-252, Original 1

OTHER REVIEW(S)

MEMORANDUM

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

DATE: April 22, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Carton/Container Labeling

APPLICATION/DRUG: NDA 022252

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

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Thursday, April 22, 2010 10:37 AM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Labeling
Follow Up Flag: Follow up
Flag Status: Red

Hi Pam,
I am in receipt of this email,
Thank you,
Mark

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

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

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

04/22/2010 10:16 AM

Hi Mark,

Please see the carton/container labeling suggestions below:

On the front of the blister label; The sponsor can move the (b) (4) name on the top (under the pills 1-7), and insert the established name (estradiol valerate) where (b) (4) is currently placed; please keep both established name in small letter to match all other labels.

On the back of the blister; The established name (estradiol valerate) can be added between (b) (4) and (estradiol valerate/dienogest) or can be placed both in one line (estradiol valerate, estradiol valerate/dienogest) with or with out parenthesis.

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

Thanks,
Pam

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

4/22/2010

10903 New Hampshire Avenue
Silver Spring, MD 20903

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

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Application
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Submission
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Submitter Name

Product Name

NDA-22252

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

Qlaira

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/s/

PAMELA LUCARELLI
04/22/2010

MEMORANDUM

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

DATE: April 15, 2010

TO: Bayer HealthCare Pharmaceuticals, Mark Rosengarten

FROM: Division of Reproductive and Urologic Products, Pamela Lucarelli

SUBJECT: Labeling Communication

APPLICATION/DRUG: NDA 022252

The correspondence below is the first labeling communication.

Lucarelli, Pamela K

From: Mark Rosengarten [mark.rosengarten@bayer.com]
Sent: Thursday, April 15, 2010 3:00 PM
To: Lucarelli, Pamela K
Subject: Re: NDA 022252 Label
Follow Up Flag: Follow up
Flag Status: Red
Attachments: FDA edits 22-252 EV DNG 4 15 10 SENT TO SPONSOR.docm

Pam

email received, please call me on my cell phone tomorrow as we discussed the number is (b) (4)

Talk to you tomorrow,

Best Mark

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

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

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

cc

Subject NDA 022252 Label

04/15/2010 02:39 PM

Hi Mark,

Attached is a redline copy of the label. Please accept the changes you agree with, and leave the ones you don't. If you have any additions, make sure you add them in another color.

Please have the label back to us by COB on 4/23/2010.

I will communicate PMC/PMR comments soon. If you have any questions, let me know. Acknowledge receipt of this email.

Pam

<<FDA edits 22-252 EV DNG 4 15 10 SENT TO SPONSOR.docm>>

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

4/16/2010

10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
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pamela.lucarelli@fda.hhs.gov

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/s/

PAMELA LUCARELLI
04/16/2010

MEMORANDUM

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

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

Date: April 1, 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
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Carrie Newcomer, Pharm.D.
Regulatory Review Officer
DDMAC

Re: **NDA 22-252**
DDMAC labeling comments for (b) (4) (estradiol valerate and dienogest)
tablets, for oral use

Background

DDMAC has reviewed the following label materials for (b) (4) (estradiol valerate and dienogest) tablets, for oral use, submitted to DRUP on July 6, 2009.

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Patient Product Information (PPI)

Please note that our comments for the draft PI are based on the substantially complete version of the draft label sent to DDMAC on March 31, 2010. Also, please note that DRISK provided comments on the draft PPI on March 23, 2010, and our comments for the draft PPI are based on the DRISK version of the PPI. DDMAC agrees with DRISK comments and offers the following additional comments.

In addition, we have considered the LoSeasonique (levonorgestrel/ethinyl estradiol tablets) PI (approved October 24, 2008) in our review of the draft (b) (4) labeling.

We offer the following comments:

PI

Please see our comments on the draft PI.

PPI

When to start TRADENAME?

(b) (4)

(b) (4)

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

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

24 pp withheld in full immed. after this page as (b)(4) Draft Labeling.

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ORIG-1

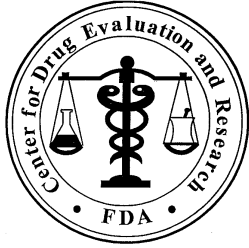
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/s/

JANICE L MANIWANG
04/01/2010



**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: March 23, 2010

To: Scott Monroe, M.D., Director
Division of Reproductive and Urologic (DRUP) Products

Through: Mary Willy, Ph.D., Deputy Director
Division of Risk Management (DRISK)
LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Robin Duer, MBA, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name: Tradename (estradiol valerate/dienogest) Tablets

Application Type/Number: NDA 22-252

Applicant/sponsor: Bayer Healthcare Pharmaceuticals

OSE RCM #: 2010-494

1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Tradename (estradiol valerate/dienogest) Tablets. The most recent version of the proposed patient labeling for this new combination oral contraceptive product was submitted on October 15, 2009. DRUP requested that we use the October 15, 2009 version of the labeling for the basis of our patient labeling review.

The initial proposed proprietary name for this product was "Qlaira", but that name was not approved. The proprietary name "Qlaira" appears in the October 15, 2009 version of the labeling for this product.

Please let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIALS REVIEWED

- Draft Tradename (estradiol valerate/dienogest) Tablets Prescribing Information (PI) submitted on October 15, 2009 and received by DRISK on March 10, 2010
- Draft Tradename (estradiol valerate/dienogest) Tablets) Patient Package Insert (PPI) submitted on October 15, 2009 and received by DRISK on March 10, 2010
- Guidance for Industry: Labeling for Combined Oral Contraceptives dated September 2007

3 RESULTS OF REVIEW

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

23 pp withheld in full immed. after this page as (b)(4) Draft Labeling.

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ORIG-1

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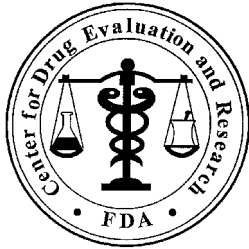
Qlaira

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/s/

ROBIN E DUER
03/23/2010

MARY E WILLY
03/23/2010
I concur



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: March 18, 2010

To: Scott Monroe, MD, Director
Division of Reproductive and Urologic Products (DRUP)

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Division Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): (b) (4)
(Estradiol Valerate Tablets, 3 mg
Estradiol Valerate and Dienogest Tablets, 2 mg/2 mg
Estradiol Valerate and Dienogest Tablets, 2 mg/3 mg and
Estradiol Valerate Tablets, 1 mg)

Application Type/Number: NDA 022252

Applicant: Bayer HealthCare Pharmaceuticals, Inc.

OSE RCM #: 2009-1756

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1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urologic Products (DRUP) for assessment of the labels and labeling for (b) (4) (Estradiol Valerate and Dienogest) Tablets from a medication error perspective. On December 22, 2009, DMEPA found the Applicant's primary proposed name, Qlaira (Estradiol Valerate and Dienogest) Tablets unacceptable. Subsequently, the Applicant submitted a secondary proposed name, (b) (4), which will be evaluated in OSE Review 2010-1755.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the label and labeling submitted as part of the September 23, 2009, submission (Appendices A and H).

3 RECOMMENDATIONS

We noted areas where information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1, *Comments to the Division*. Section 3.2, *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be 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 questions or need clarifications, please contact OSE Project Manager, Maria Wasilik, at 301-796-0567.

3.1 COMMENTS TO THE DIVISION

A. *Product Design*

If approved, (b) (4) will be the first four-phase oral contraceptive in the US. The four-phase design of this product is unique and the initiation of therapy and the instructions for missed tablets are different than what is considered common practice for birth control pills. Birth control pills typically provide the option of two start dates (Sunday or first day of menstrual cycle). Also, when a pill is missed, it can be taken as soon as a patient remembers or the patient can double up the pill the next day. These dosing instructions are well established and ingrained in both healthcare practitioners' and patients' mindsets when administering birth control pills. These differences are likely to lead to confusion and medication errors. Therefore, we recommend the product instructions for initiation of therapy and missed doses must be aligned with currently marketed birth control pills. If this cannot be accomplished for some clinical reason, then the Applicant will have to educate healthcare practitioners and patients and reverse the established practice for birth control pill administration. Healthcare practitioners and patients will need to understand the unique differences between (b) (4) and other oral contraceptive in regards to initiation of therapy and remedying missed doses. This will be a difficult task given the long standing practice for this class of product.

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

B. All Labels and Labeling

The current presentation of the established name implies that this product is a single combination tablet that contains Estradiol Valerate and Dienogest. However, this product contains 4 phases. Each phase has different active ingredients and strengths. DMEPA recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC) and Tarun Mehta, the assigned Office of New Drug Quality Assessment (ONDQA) Chemist, regarding the expression of the established name of this product.

C. Insert Labeling

1. General Comments

Revise the insert to describe the last two tablets as inert in the Highlights of Prescribing Information (Dosage Forms and Strengths) and Full Prescribing Information (Dosage Forms and Strengths – Section 3, Description – Section 11, How Supplied – Section 16.1, and Information for Patients – Section 17.1).

2. Dosage and Administration – Section 2.1

We note the use of the abbreviation, COC. To prevent misinterpretation and confusion, revise the sentence to read ‘combination oral contraceptive’. We do not recommend the use of abbreviations in the approved labeling of products because they can be misinterpreted and adopted by physicians when prescribing. This carryover to prescribing has resulted in misinterpretation and wrong drug errors.

(b) (4)



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

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/s/

JIBRIL ABDUS-SAMAD
03/18/2010

DENISE P TOYER
03/18/2010

CAROL A HOLQUIST
03/18/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 5, 2010

TO: Pam Lucarelli, Regulatory Project Manager
Gerald Willett, M.D., Medical Officer
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-252

APPLICANT: Bayer HealthCare Pharmaceuticals, Inc.

DRUG: Qlaira (estradiol valerate/dienogest tablets)

NME: No

THERAPEUTIC
CLASSIFICATION: Standard Review

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

CONSULTATION
REQUEST DATE: September 2, 2009

DIVISION ACTION
GOAL DATE: May 6, 2010

PDUFA DATE: May 6, 2010

I. BACKGROUND:

This application was submitted in support of the use of estradiol valerate/dienogest (Qlaira) for the prevention of pregnancy and the treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception. Four pivotal studies were submitted in support of the application, and all four inspected.

The conduct of the following protocols was inspected:

Protocol 304742 entitled "A Multicenter, Open-label, Uncontrolled Study to Investigate the Efficacy and Safety of a 4-phasic Oral Contraceptive SH T00658ID Estradiol Valerate/Dienogest in a 28-day Regimen for 13 Cycles in Healthy Female Subjects", and

Protocol 306660 entitled "Multi-center, Open, Uncontrolled Study to Investigate the Efficacy and Safety of a 4-phasic Oral Contraceptive SH T00658ID Containing Estradiol Valerate and Dienogest in a 28-day Regimen for 20 Cycles in 1200 Healthy Female Volunteers" and

Protocol 308960 entitled "A Multicenter, Double Blind, Randomized, Parallel-Group, Placebo-Controlled, 7 Cycle Duration (196 Days), Phase 3 Study of Oral Estradiol Valerate/Dienogest Tablets for the Treatment of Dysfunctional Uterine Bleeding", and

Protocol 308961 entitled "A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, 7 Cycle Duration (196 Days), Phase3 Study of Oral EstradiolValerate/Dienogest Tablets for the Treatment of Dysfunctional Uterine Bleeding".

Protocol 304742

The objective of this study was to evaluate the contraceptive efficacy, cycle control, safety and tolerability of SH T00658ID in women 18 to 35 years of age over a period of 13 treatment cycles.

The primary efficacy variable was the number of observed pregnancies.

Protocol 306660

The primary objective was to confirm safety and efficacy of SH T00658ID in women of 18 to 50 years of age.

The primary efficacy parameter was the number of pregnancies observed.

Protocol 308960

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Olga Hlavackova, M.D. Gynekologicka ambulance Zeyerova 2442 Pisek 39701 Czech Republic Phone # +420382211 50	308961/ 16	30 Nov-4 Dec 2009	NAI
Klaus Greven, M.D. Pfarrstrasse 47 D-30459 Hannover Germany Phone # +49 (0) 511 4102870	306660/ 120/	1-4 Feb 2010	Pending: Interim classification: NAI
Rafael Sanchez Borrego, M.D. CENTRE ASSISTENCIAL NTRA. SRA. DE BRUGUES Crta. A Sta. Creu de Calafell, i 00 08850 Gava Barcelona Spain Phone # 34 (0) 93638 1482	306660/ 33/	30 Nov-4 Dec 2009	VAI
Damon Raskin, M.D. Blue Hil Medical Group 881 Alma Real Drive, Suite 320 131 Pacific Palisades, CA 90272 Phone # 310.459.4333	308960/ 13/	16 Nov 2009-11 Jan 2010	NAI
Lisa Gidday, M.D. Clinical Trial Center of Colorado 8199 SouthPark Lane, Suite 100 Littleton, CO 80120 Phone # 303.730.3332	3047421/ 26/	2-9 Nov 2009	VAI
Sponsor Bayer HealthCare Pharmaceuticals, Inc. P.O. Box 1000 Montville, NJ 07045	304742, 308961, 306660, and 308960/	2 Nov-9 Dec 2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Olga Hlaváčková, M.D.

Gynekologická ambulance

Zeyerova 2442

Písek, Czech Republic

a. What was inspected: At this site, the study records for all 16 randomized subjects were audited for the following parameters which included, but were not limited to, inclusion/exclusion criteria, primary and secondary endpoints, clinical laboratory results, development of related and unrelated illnesses, adverse event reporting, subject discontinuations, subject eligibility, informed consent, test article accountability, ethics committee approvals, monitoring records, electronic case report forms, concomitant medications, and adherence to protocol-specified procedures for blinding and randomization.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: Data appear acceptable in support of the respective application.

2. Klaus Greven, M.D.

Pfarrstrasse 47

D-30459 Hannover

Germany

a. What was inspected: At this site, 120 subjects were screened and enrolled, with 92 subjects completing the study through nine visits. All 120 records were reviewed for appropriate informed consent. The study records for 30 subjects were reviewed in depth for the following parameters which included, but were not limited to, study eligibility, adverse events, drug accountability, and monitoring activities.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR). Data appear acceptable in support of the respective application.

3. Rafael Sanchez-Borrego, M.D.
Centre Assistencial Ntra Sra de Burgues
Ctra. A Sta. Creu de Callafell 100
Gava (Barcelona), Spain

- a. What was inspected:** At this site, 33 subjects were screened and randomized to the study, with 20 subjects completing the study. The study records for all subjects were reviewed with respect to the primary efficacy endpoint and informed consent. Other records reviewed included, but were not limited to, adverse event reporting, laboratory data, discontinued subjects, ethics committee documentation, site monitoring reports, case report forms, source documents, and drug accountability.
- b. General observations/commentary:** A Form FDA 483 was issued. Inspection revealed that a pregnancy that occurred within three month's of the subject's discontinuation from the study was not followed to outcome, and that pregnancy letters were not sent to the 13 subjects who discontinued early from the study, all being requirements of the protocol.

Dr. Sanchez-Borrego responded adequately to the inspectional findings in a letter dated December 14, 2009. He stated that pregnancy letters were sent to the 13 subjects who discontinued early; however, he acknowledged, that this was not documented.

- c. Assessment of data integrity:** Although regulatory violations were noted, they are unlikely to affect data integrity in a substantive manner. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Damon Raskin, M.D.
Blue Hil Medical Group
881 Alma Real Drive, Suite 320
Pacific Palisades, CA 90272

- a. What was inspected:** At this site, 67 subjects were screened, 13 were randomized, and 10 completed the study. All 67 subject records were audited with respect to informed consent. The study records of the ten completing subjects were reviewed in depth with respect to source documents, electronic Case Report Forms (eCRFs), inclusion criteria, laboratory tests, concomitant therapies, screening and enrollment logs, test article accountability, monitoring reports, and adverse event reporting.
- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

5. Lisa Gidday, M.D.
Clinical Trial Center of Colorado
8199 SouthPark Lane, Suite 100
Littleton, CO 80120

- a. What was inspected:** At this site, of the 26 subjects that were screened, 24 were enrolled, and 14 completed the study. All 26 subject records were audited with respect to informed consent documents, inclusion/exclusion criteria, source documents, case report forms, physical examinations, subject diaries, and laboratory analyses.
- b. General observations/commentary:** A Form FDA 483 was issued. Inspection revealed that 14 subjects did not have gynecological examinations performed at Visit 6 as required by protocol. Not all adverse events were reported appropriately, and some record keeping discrepancies were also evident.

Dr. Gidday adequately responded to the inspectional findings in a letter dated November 13, 2009.

- c. Assessment of data integrity:** Although regulatory violations were noted, they do not appear to be pervasive findings, and are unlikely to importantly impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

6. Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045

- a. What was inspected:** The sponsor's study activities with regard to the four protocols listed above were audited, including a review of the firm's organization and personnel, the process by which clinical investigators were selected and monitored, monitoring procedures and activities, adverse event reporting, data collection and handling including automated clinical data entry, and test article storage and accountability.
- b. General observations/commentary:** A Form FDA 483 was issued. Inspection revealed that monitoring reports were submitted late and that monitoring visits did not occur with the frequency required in the monitoring plan, and that the records detailing the final disposition of the investigational product were not adequate with respect to batch numbers, lot numbers, and/or dates.

Bayer responded adequately to the items listed on the Form FDA 483 in a letter dated December 18, 2009.

- c. Assessment of data integrity:** The deviations noted immediately above would not appear to have a significant impact on data integrity, and the data submitted by the sponsor appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Hlavackova, Greven, Borrego, Raskin, and Gidday were inspected in support of this NDA. Although regulatory violations were noted at the sites of Drs. Borrego and Gidday, the findings are unlikely to impact data integrity. Similarly, the inspection of the sponsor, Bayer, revealed regulatory violations that are unlikely to affect data integrity. The studies appear to have been conducted adequately, and the data generated by the clinical sites and submitted by the sponsor appear acceptable in support of the respective indication.

Please note that the final classification of the inspection of Dr. Greven's site is pending receipt and review of the EIR. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application
Type/Number

Submission
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Product Name

NDA-22252

ORIG-1

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HEALTHCARE
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LS INC

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/s/

ROY A BLAY
03/05/2010

TEJASHRI S PUROHIT-SHETH
03/05/2010

DSI CONSULT: Request for Clinical Inspections

Date: September 2, 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: Gerald Willett, 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 22-252 Qlaira (estradiol valerate/dienogest tablets)

I. General Information

Application#: NDA 22-252
Applicant: Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045
Contact: Sharon Brown – Director, Global Regulatory Affairs
Phone: (973) 487-2162
E-mail: Sharon.Brown@bayer.com

Drug Proprietary Name: Qlaira (estradiol valerate/dienogest tablets)
NME: Yes
Review Priority: Standard

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

Proposed New Indication(s): Primary Indication: Prevention of pregnancy
Secondary Indication: Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception

PDUFA: May 6, 2010
 Action Goal Date: May 6, 2010
 Inspection Summary Goal Date: March 6, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 103/104 Olga Hlavackova Gynekologicka ambulance Zeyerova 2442 Pisek 397 01, Czech Republic Phone # 42.0.382.21.50.00	Protocol 308961	Enrolled 16 Subjects	Heavy Menstrual Bleeding
Site # 123 Damon Raskin Blue Hill Medical Group 881 Alma Real Drive Suite 103 Pacific Palisades, CA 90272 Phone # 310.459.4333	Protocol 308960	Enrolled 13 Subjects	Heavy Menstrual Bleeding
Site # 20 Klus Greven Pfarrstrasse 47 30459 Hannover, Germany Phone # 49.0.511.410.28.70 Fax # 49.0.511.410.28.733	Protocol 306660	Enrolled 120 Subjects	Prevention of Pregnancy
Site # 82 Sanchez Borrego Diatros Gava Avda. Mas Sellares 16 08850 Gava (Barcelona) Phone # 34.0.936.62.05.00 Fax # 34.0.936.38.39.49	Protocol 306660	Enrolled 33 Subjects	Prevention of Pregnancy
Site # 520 Lisa Giddy Arapahoe Internal Medicine, PC 8199 South Park Lane Suite 100 Littleton, CO 80120 Phone # 303.730.3332	Protocol 304742	Enrolled 26 Subjects	Prevention of Pregnancy

III. Site Selection/Rationale

We are requesting a DSI consult because dienogest (DNG) is a New Molecular Entity (NME). We believe it is necessary to access one foreign site and one domestic site for the heavy menstrual bleeding indication and two foreign sites and one domestic site for the prevention of pregnancy indication.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- 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):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (Enrollment of large numbers of study subjects and this would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons:

- This product is an NME
- There are two indications being studied (prevention of pregnancy and heavy menstrual bleeding)

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Should you require any additional information, please contact Pam Lucarelli, Regulatory Health Project Manager at 301-796-3961 or Dr. Gerald Willett, Medical Officer at 301-796-1024.

Concurrence: (as needed)

___Gerald Willett M.D. _____ Medical Team Leader
___Lisa Soule M.D. _____ Medical Reviewer
___Scott Monroe M.D. _____ Division Director (for foreign inspection
requests or requests for 5 or more sites only)

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

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

/s/

PAMELA LUCARELLI
09/09/2009

LISA M SOULE
09/11/2009

SCOTT E MONROE
09/11/2009
I concur with this request.