DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022252/Original 1 **NDA APPROVAL**

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Sharon W. Brown
Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Brown:

Please refer to your July 2, 2009 New Drug Application (NDA), received July 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Natazia (estradiol valerate and estradiol valerate/dienogest) Tablets.

We acknowledge receipt of your submissions dated July 14, August 11, September 23 and 30, October 13 and 15, November 3, 6, 13, and 24, and December 18 and 21, 2009; and February 1 (3), March 9, 17, and 30, April 7, 8, 9, 20, 22, 23 (2), 26 and 27, May 3 (2), 4 (2), 5, and 6 (2) 2010.

NDA 022252 provides for the use of Natazia (estradiol valerate and estradiol valerate/dienogest) Tablets (b) (4) we have designated as follows:

- NDA 022252/Original 1 - prevention of pregnancy.
- (b) (4)

The subject of this action letter is NDA 022252/Original 1. (b) (4)

We have completed our review of NDA 022252/Original 1, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your application was not referred to an advisory committee because the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on May 6, 2010 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022252**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with Final Printed Labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because pre-menarcheal patients are not at risk of becoming pregnant and the use of this product before menarche is not indicated. We note that you have fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult data.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies

and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of venous thromboembolic events or arterial thromboembolic events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1637-1. A prospective, controlled, non-interventional, long-term cohort study that follows a series of cohorts consisting of new users of Natazia (estradiol valerate and estradiol valerate/dienogest) tablets and new users of oral contraceptives containing other progestins. This study should be conducted by expanding the ongoing European postmarketing comparative safety surveillance study entitled *International Active Surveillance Study of Women Taking EV/DNG* (INAS-EV) to include US women. The expanded study should enroll a total of at least 50,000 women in the US and Europe, who will be followed for at least three years. The primary objective of the study is to assess the thrombotic risks of short and long-term use of Natazia (estradiol valerate and estradiol valerate/dienogest) tablets and of other oral contraceptives in a study population representative of the actual users of the individual products. The main clinical outcomes of interest are deep venous thrombosis (DVT), pulmonary embolus (PE), acute myocardial infarction, and cerebrovascular accidents. There should be no age restrictions for entry into the study and the study should include younger users (i.e., women less than 18 years of age).

The timetable you submitted on May 4, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2010
Study Completion Date:	September 2015
Final Report Submission:	September 2016

Interim reports are to be submitted annually, after enrolled subjects have completed one and two years of participation.

Submit the protocol to your IND, with a cross-reference letter to NDA 022252. Submit the final report to NDA 022252. Prominently identify each submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**

- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Pamela Lucarelli, Regulatory Health Project Manager, at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

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

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

/s/

JULIE G BEITZ
05/06/2010