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Worldwide Regulatory Affairs

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1496 '03 APR -1 A9:28

March 31, 2003

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD, 20852

RE: Comment on Dockets No. 03D-0007, CDER 2002173
Draft Guidance for Industry on Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptom-Recommendations for Clinical Evaluation (FR Doc. 03-02213)

Dear Sirs:

Wyeth Pharmaceuticals Inc (Wyeth), hereby submits comments to Docket No. 03D-0007, pertaining to the "Draft Guidance for Industry on Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation" published in the *Federal Register*, Volume 68, Number 21, pages 5025-5026 (January 31, 2003).

Wyeth is a major research-orientated pharmaceutical company with leading products in the areas of women's health care, cardiovascular disease therapies, central nervous system drugs, anti-inflammatory agents, anti-infective agents, vaccines, and biopharmaceuticals. Wyeth is one of the world's largest research-based pharmaceutical and healthcare products companies, and is a leading developer, manufacturer and marketer of prescription drugs and over the counter medications.

Wyeth acknowledges the Agency's efforts to provide further recommendations to industry for the development of studies for the clinical evaluation of estrogen/progestin containing drug products to treat vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA) symptoms at this crucial time. Wyeth fully supports the overall goals of developing safe and effective estrogen and estrogen/progestin products and defining their appropriate conditions of use.

The following are Wyeth's views on the aforementioned draft guidance. Wyeth's suggestions for text changes will be illustrated by underlined text for additions and ~~strikethrough text~~ for deletions.

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III. Drug Products Containing Estrogen Alone

III. A. Indications

Line 71: For clarity, Wyeth suggests the following change of text:
Patient self-assessed symptoms based on the severity of vulvar and vaginal atrophy at baseline include:

Line 77: For consistency with the scale used to evaluate the other four VMS symptoms, Wyeth suggests the following change:

Vaginal bleeding associated with sexual activity ~~(presence vs. absence)~~ (none, mild, moderate or severe)

III.B: Study Considerations

Line 86-87: Wyeth suggests the following change of text:
In addition, we recommend that the doses included in the dose range study may include an ineffective dose as one of the doses evaluated, or the sponsor may include a rationale justifying their selection of the lowest effective dose.

Rationale: The dose range studied should be able to provide information with regard to the lowest effective or ineffective dose. Justification for the selection of lowest effective dose may be based on trend analysis of data. Therefore, it should not be mandated to include an ineffective dose as one of the doses evaluated but an option should be given to include either an ineffective dose or rationale justifying the selection of lowest effective dose.

III. C: Inclusion and Exclusion Criteria

Line 106: To clarify, Wyeth suggests the following change of text:
For the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, study participants be enrolled who have self-identified at baseline at least one moderate to severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear or have a vaginal pH > 5.0.

Lines 112-115: Wyeth suggests the minimum washout period be eight weeks or longer for prior vaginal hormonal products (rings, creams, gels), prior

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transdermal estrogen alone or estrogen/progestin products, prior oral estrogen or estrogen/progestin products and prior intrauterine progestin therapy.

Rationale: There is limited data supporting 1 week washout period for prior vaginal hormonal products, or 4 week washout for prior transdermal estrogen alone or estrogen/progestin products. For consistency and to ensure return to baseline, Wyeth suggests a minimum washout period of eight weeks for the therapies listed above. It would be highly unlikely that a women who was on hormonal vaginal cream therapy for an atrophic vagina for an extended period of time, could return to baseline in one week.

III.D: Monitoring

Lines 139-140: Wyeth suggests modification to the hemostatic measures as specified below to include measures of procoagulant, anticoagulant, fibrinolytic, antifibrinolytic factors and products of coagulation such as: Factor V Leiden (at baseline only), antithrombin III activity, Protein S antigen, Protein C antigen, Factor VII clotting, fibrinogen, plasminogen activator inhibitor antigen (PAI-1) and prothrombin fragment F1 +2.

Rationale: Wyeth suggests a more complete hemostatic profile for a comprehensive assessment of the elements of hemostatic balance.

III.E: Primary Endpoints

Lines 142-154: Wyeth suggests that only one primary endpoint be used for the basis of approval for the treatment of VMS indication: mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12. The other three listed may be used as secondary endpoints. For clarity, Wyeth also suggests changing the term **frequency** to **number of flushes.**

Rationale: The single suggested primary clinical endpoint is easy to measure and is clinically meaningful. In addition, multiple primary endpoints will complicate the statistics by introducing p-value adjustments for what is an otherwise straightforward clinical evaluation.

Lines 156-163: Wyeth suggests one primary endpoint for moderate to severe VVA:

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her.

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[However, mean change may not be appropriate depending on which evaluation scale is used: 2, 3 or 4 categories (none, mild, moderate or severe)].

Plus one of the following as secondary endpoints:

- Mean change from baseline to week 12 in vaginal pH

- OR -

- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells)

Rationale:

1) Patient's assessment of improvement in the most bothersome symptom is the best indicator of a drug's benefit.
2) The other measurable endpoints (secondary) could be used as supportive data.

Additional Comment:

- The most appropriate analysis of pH and superficial cells may be based on transformed data (pH) or may be nonparametric (superficial cells and parabasal cells) so mean changes may not be the best summary statistic.

IV. Drug Products Containing Estrogen Plus Progestin

IV. C: Inclusion and Exclusion Criteria

Lines 235-236: Wyeth suggests patients with biopsies at study entry evaluated as "No Tissue" or "Tissue insignificant for diagnosis" may be included in the study at the sponsor's risk.
Rationale: Based on our clinical trial experience, approximately 12% of patients are excluded from studies due to screening biopsy diagnoses of "No Tissue" or "Tissue insignificant for diagnosis." Many postmenopausal women have atrophic endometrium. There is a minimal chance of having an endometrial hyperplasia, in cases where adequately performed biopsies are performed, where "no tissue" or "tissue insignificant for diagnosis" is obtained.

IV. D: Monitoring

Lines 258-260, 276-282: With the objective in mind of helping to ensure a consistent evaluation of endometrial safety throughout the study, Wyeth

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suggests the following approach to be used in the reading of endometrial biopsies

- Any two of the three blinded, expert, primary pathologists initially assess the slides from the endometrial biopsies obtained either at screening or because of participant bleeding while on study drug (safety reading).
- Baseline evaluation of endometrial biopsies:
  - If either of the two primary pathologists assess a baseline biopsy as any hyperplasia or cancer, that subject will be excluded from the study and receive counseling from the investigator for the recommended follow-up.
- Evaluation of endometrial biopsies:
- Two pathologists, preferably the same two that performed the baseline evaluation, should evaluate any interim endometrial biopsies and the endometrial biopsies obtained because of participant bleeding while on study drug (safety reading).
- The biopsies will first be evaluated based upon the presence or absence of hyperplasia. If an initial determination of hyperplasia is made, the presence or absence of atypia must then be made.
- If cancer is diagnosed at any reading, the final determination whether cancer is present should be based on a more definitive pathological specimen (e.g. hysterectomy, D&C) and that subject will be removed from the study and receive counseling from the investigator for the recommended follow-up.
- Determination of Hyperplasia:
- If the two pathologists agree to the absence of hyperplasia, the patient is considered "normal" and therefore agreement on the histologic state of a normal endometrium is not required.
- If the two pathologists agree to the presence of hyperplasia, the presence or absence of atypia must then be determined (see determination of atypia).
- If the pathologists disagree upon the presence or absence of hyperplasia, a third pathologist will adjudicate. The final determination of the presence or absence of hyperplasia will be based on the majority diagnosis. If the two pathologists agree to the presence of hyperplasia, the presence or absence of atypia must then be determined (see determination of atypia).

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- Determination of atypia:
- If any two pathologists agree to the presence of hyperplasia, the presence or absence of atypia must be determined.
- If the two pathologists disagree upon the presence or absence of atypia, a third pathologist will adjudicate. The final determination of the presence or absence of atypia will be based on the majority diagnosis.

Rationale: Wyeth's proposal may offer advantages because the same two pathologists that read the screening biopsies should also read the same patient's biopsies throughout the study, if possible. When on therapy, a third pathologist's opinion is solicited to adjudicate when there is a difference of opinion between the first two pathologists regarding the presence or absence of hyperplasia and the presence or absence of atypia in patients diagnosed with hyperplasia. Wyeth believes that this approach to the diagnosis of a potentially serious situation is methodical, conservative and in the best interest of patient safety.

Lines 287-288: Digital recording of diagnostic areas of the slides, or the biopsy slides with the diagnosed areas be made available upon FDA request.

***Rationale*:** Wyeth acknowledges the importance of having the diagnosed area available for FDA review. However, sites may not possess the appropriate equipment to provide digital images and this should not be necessary if biopsy slides are available.

Lines 289-292: Any new findings noted during the conduct of the study and on end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation. Subject will be monitored ~~until there is complete clinical resolution of any diagnosed condition~~. and receive counseling from the investigator for the recommended follow-up.

Lines 293-294: Same as III.D: Monitoring, Lines 139-140.

IV. F: Study Analysis

Lines 308-311: Wyeth suggests that the estimated risk of endometrial hyperplasia after 1 year treatment with estrogen/progestin treatment be changed to 1-2% for women treated with currently marketed combination estrogen/progestin drugs. Wyeth also suggests that the results from the clinical trial demonstrate a hyperplasia rate that is $\leq 2\%$ with an upper bound of the

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one-sided 95 percent confidence interval for that rate which does not exceed 4%.

Rationale: Wyeth suggests the above modification, in an effort to harmonize global regulatory practice, and to be consistent with the European Guidance: "CPMP's Points to consider on Hormone Replacement Therapy" (November 1997), which has been in place for several years. This view is supported by many leading clinical researchers and considered a standard approach to evaluating the risk of endometrial hyperplasia.

This letter is submitted in duplicate. Wyeth appreciates the opportunity to provide this constructive input to the rulemaking process. Please contact me by telephone (484- 865-3722) or by facsimile (484-865-9214) or Paul Scrimo by telephone (484-865-3756) if there are any questions regarding the submitted comments.

Sincerely,

Vijay Tammara, Ph.D.
Associate Director II, Worldwide Regulatory Affairs
Wyeth Pharmaceuticals Inc.