Eli Lilly and Company

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

Re: Docket Number 03D-0007; Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation

Eli Lilly and Company (Lilly) appreciates the opportunity to comment on this proposed Guidance for Industry. We support FDA's desire to update its March 1995 *Guidance for Clinical Evaluation of Combination Estrogen/Progestin – Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women.*

Lilly commends FDA on the proposed guidance's emphasis with regard to addressing the reduction of the risk of endometrial hyperplasia or adenocarcinoma from estrogen exposure in women who have a uterus. In the wake of the Women's Health Initiative (WHI) report and modification of the protocol relative to the estrogen/progestin combination arm, Lilly fully supports updating this guidance with the most current understanding of potential risks and benefits of estrogen and estrogen/progestin therapy to treat women.

Several Lilly physicians and other researchers carefully examined this guidance, and have some concerns and recommendations for consideration by FDA. First, in Section III(A)(1), FDA articulated very clear definitions of mild, moderate and severe vasomotor symptoms similar to the 1995 guidance. Lilly recommends that FDA include similar descriptions to clarify the terms "none, mild, moderate or severe" used in defining patient self-assessed symptoms of vulvar and vaginal atrophy in Section III(A)(2).

Second, Lilly has 3 recommendations regarding the Inclusion and Exclusion Criteria defined in Sections III(C) and IV(C).

1) Either modification of the penultimate bullet, or a separate bullet, that would recommend exclusion of women with previous history of estrogen-dependent malignancy (e.g., breast or uterus). The current bullet focuses only on prior breast cancer.
2) Addition of a bullet that recommends exclusion of women with a previous cardiovascular event (e.g., stroke, myocardial infarction, and acute coronary syndrome) or increased cardiovascular risk equivalent (e.g., diabetes). Lilly believes that there has been sufficient demonstration of the cardiovascular risks associated with estrogen and estrogen/progestin combinations to exclude women at such risk.

3) Addition of a bullet that recommends exclusion of women with a previous history of thromboembolic disorder because of the increased risk associated with use of estrogen and estrogen/progestin combinations.

Third, Lilly recommends that the safety assessments defined under Section III(D) and IV(D) include an assessment of "inflammatory markers (e.g., prothrombotic mutation G20210A, lupus anticoagulant, anticardiolipin antibodies)." This could be added to the bullet that currently lists the "safety assessments of lipids and of carbohydrate and coagulation parameters." This addition will guide clinical investigators in the same way listing coagulation parameters does.

Finally, under Section III(E), Lilly is concerned that the proposed co-primary endpoints exclude the evaluation of clinical (physical) evidence of efficacy. FDA's recommendation on co-primary endpoints reflects a major improvement over the 1995 guidance. However, Lilly believes that part of the acceptable endpoint algorithm should include clinical or physical evaluation of vulvar and vaginal atrophy. Neither vaginal pH nor vaginal maturation index correlate with symptoms or clinical findings of vulvar and vaginal atrophy. Lilly recommends the co-primary endpoints include <u>one</u> of the two objective evaluations, vaginal pH OR vaginal maturation index, in addition to the patient's assessment **and** clinical findings, as in the following:

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

- *Mean change from baseline to week 12 in clinical (physical) findings in vulvar and vaginal atrophy*

and EITHER

- 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)

Again, we appreciate the opportunity to comment on the details of the proposal, and applaud FDA's initiative to update this guidance.

Sincerely,

ELI LILLY AND COMPANY

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