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Beth Rosenshein



Re: Docket No. 2004P-0513/PRC1

Dear Ms. Rosenshein:

This letter responds to your petition for reconsideration (PRC) dated February 27, 2006, regarding the denial of your citizen petition requesting changes to the labeling for Premarin.

You request reconsideration of the Food and Drug Administration's (FDA's) January 30, 2006, decision to deny your original citizen petition (2004P- 0513). In your original petition, you requested that FDA make the following two changes to the labeling for Premarin (conjugated estrogens) tablets:

- Update the black box warning **ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER** in the prescribing information for all strengths of Premarin tablets to recognize significant prolonged levels of equilin after withdrawal of estrogen therapy.
- Add the following statements to the warnings section of the labeling for Premarin tablets:

**PROLONGED EXPOSURE TO EQUINE ESTROGENS  
CONTINUES FOLLOWING CESSATION OF ESTROGEN  
THERAPY**

Equine estrogens can accumulate during Premarin therapy. It has been shown that equine estrogens have a prolonged presence after estrogen therapy has stopped. Premarin contains estrogens which can accumulate. Significant amounts of equilin and its metabolites may be present for at least 3-6 months after estrogen therapy has ended.

The Commissioner may grant a petition for reconsideration if the Commissioner determines the petition to be in the public interest and in the interest of justice (21 CFR 10.33(d)). Section 10.33(d) provides that the Commissioner will grant a petition for

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reconsideration if the Commissioner determines all of the following apply:

- (1) The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.
- (2) The petitioner's position is not frivolous and is pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting reconsideration.
- (4) Reconsideration is not outweighed by public health or other public interests.

FDA has considered the information submitted in your petition for reconsideration, and for the reasons explained below, FDA upholds its previous decision to deny the citizen petition.

#### **I. GROUNDS FOR RECONSIDERATION**

You request reconsideration of your original petition because you state that "[t]he issues that were raised to refute the importance of [your] original request" did not address the clinical significance of elevated levels of equine estrogens and their prolonged presence after cessation of therapy in several ways. Specifically, you address the following statements in FDA's denial of your citizen petition:

- You disagree with FDA's statement that the use of equine estrogen does not result in a different endometrial risk profile than the use of human estrogens of an equivalent estrogen dose.
- You disagree with FDA's conclusion that you have not provided reasonable evidence of an association of a serious hazard with a drug that would warrant adding specific warnings on the accumulation of equine estrogens.
- You disagree with FDA's footnote indicating our understanding that the amount of circulating levels of equilin does not generally dictate a health care practitioner's decision as to which type of treatment for breast cancer is optimal in any particular situation.

You also comment on FDA's analysis of the references you submitted in support of your original citizen petition.

## II. DISCUSSION

We have reviewed the information submitted in support of your original petition and our responses and conclusions to your original petition.

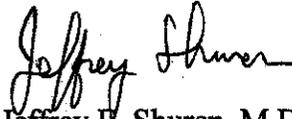
We conclude that the relevant information and views in the administrative record were adequately considered when we reviewed and denied your original citizen petition. We also conclude that the data and information submitted in support of your original petition and reconsideration request are not sufficiently persuasive to cause us to modify or overrule the Agency's decision on your citizen petition.

## III. CONCLUSION

After a review of the information provided in your reconsideration request, we conclude that the relevant information and views in the administrative record were adequately considered when we reviewed and denied your citizen petition.

The decision to deny the citizen petition is upheld.

Sincerely,



Jeffrey E. Shuren, M.D., J.D.  
Associate Commissioner for Policy and  
Planning