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**SYNTHETIC CONJUGATED ESTROGENS:  
MAY 5, 1997  
QUESTIONS AND ANSWERS**

**1. WHAT IS PREMARIN?**

Premarin is the brand name of conjugated estrogens, manufactured by Wyeth-Ayerst, and derived from the urine of pregnant mares.

**2. WHO TAKES PREMARIN AND WHY?**

More than 8 million American women take Premarin each year for estrogen replacement to treat symptoms of menopause or to prevent and treat osteoporosis.

**3. IS PREMARIN SOMEHOW BETTER THAN OTHER ESTROGEN PRODUCTS? IF NOT, WHY IS IT SO WIDELY PRESCRIBED?**

Premarin is different from other estrogen products in that it is the only brand of conjugated estrogens marketed in the U.S. Other drugs approved for hormone replacement therapy contain different types of synthetic estrogens, including dienestrol, estradiol, esterified estrogens, and estropipate. Despite the different composition of these drugs, they have all been demonstrated to be safe and effective for the treatment of menopausal symptoms and many of them have been found to be safe and effective for prevention of osteoporosis too. Premarin has not been demonstrated to be superior to other marketed products.

Various factors affect the prescribing habits and preferences of physicians. Among these are manufacturer's advertising and promotional techniques as well as patient's knowledge and request for commonly used products.

**4. WHAT IS A GENERIC DRUG?**

A generic drug is a "copy" of a brand-name drug. The Federal Food, Drug, and Cosmetic Act (FD&C Act) states that the application for marketing a generic drug, called an Abbreviated New Drug Application or ANDA, must contain, among other things, information to show that the active ingredient of the new drug is the same as that of the listed drug. The Act goes on to say that the generic copy should be approved for marketing unless "the information

submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug."

#### **5. HOW IS A GENERIC DRUG EVALUATED AND APPROVED?**

The FD&C Act requires that a generic copy contain, among other things, the same active ingredients as the reference listed drug (usually the innovator or brand name drug.) Additionally, the generic copy must be demonstrated to be bioequivalent to -- that is, shown to be absorbed and used by the body in the same way as -- the reference listed drug.

New, or innovator, drugs require an evaluation of safety and effectiveness in human trials. Generic drug manufacturers are not required to replicate this extensive clinical testing. Instead, a generic drug must be shown to be the same as the innovator drug and, therefore, can be expected to have the same effects as the innovator drug.

The Center for Drug Evaluation and Research (CDER) reviews generic drug marketing applications. Scientific staff in CDER review all applications for their scientific content, manufacturing procedures, and labeling claims.

#### **6. WHAT IS CDER'S POSITION ON GENERIC PREMARIN?**

CDER concludes that an abbreviated new drug application (ANDA) for a synthetic version of Premarin cannot be approved at this time because the active ingredients in Premarin have not yet been adequately defined.

#### **7. DOESN'T A GENERIC PRODUCT JUST HAVE TO CONFORM TO THE CURRENT USP DRUG SUBSTANCE MONOGRAPH?**

To be approved for marketing, a generic product must have the same active ingredients as the reference listed drug. Compliance with the USP monograph is not a legal requirement for the approval of an ANDA, nor is compliance with the monograph necessarily sufficient to determine whether the statutory requirements of the FD&C Act for the approval of a generic drug have been fulfilled. FDA applies current scientific knowledge in making its approval decisions, even if that knowledge has not yet been incorporated into the USP monograph.

#### **8. FDA HAD CONSISTENTLY SUPPORTED THE POSITION TAKEN IN THE 1970 USP MONOGRAPH THAT THE INGREDIENTS SODIUM ESTRONE SULFATE AND SODIUM EQUILIN SULFATE ARE THE SOLE ACTIVE INGREDIENTS IN PREMARIN. DOESN'T THIS REVERSE THAT POSITION?**

Yes. At the time of publication of the monograph in 1970, little information was available on the effects of

estrogens on bone and the estimates of estrogenic potency of Premarin components were derived from clinical studies of menopausal symptoms. In addition, data on the detailed composition of Premarin and the pharmacologic activity of its components were limited. In fact, at the time, much of the available data indicated that many compounds found in Premarin were present in small amounts, and had weak estrogenic activity -- characteristics associated with impurities. Premarin was, therefore, defined in terms of the total estrogenic potency of the two active ingredients rather than the sum of the potencies of various components.

Since that time, emerging scientific evidence demonstrates that all estrogens do not exert their effects in a uniform manner with respect to different target tissues. Newer analytical techniques applied to determine the composition of Premarin now demonstrate that it consists of a mixture of a substantial number of compounds with potential pharmacologic activity. Clinical studies performed since publication of the USP monograph reveal that the assigned potencies of the components of Premarin tablets do not correctly reflect their relative potencies, and that at least one ingredient, previously believed to be an impurity, actually generates a significant concentration of a potentially active metabolite.

Based on new scientific information as well as improved techniques for compositional analysis, CDER can no longer support the position taken in the current USP monograph.

**9. WHAT DATA HAVE BEEN SUBMITTED TO DEMONSTRATE THAT AN APPROVED ANDA MEETING THE USP MONOGRAPH FOR SYNTHETIC CONJUGATED ESTROGENS TABLETS WOULD NOT PROVIDE THE SAME CLINICAL EFFECTS AS PREMARIN?**

The statute does not require that the generic drug have the same clinical effects, nor does it require clinical trials demonstrating the generic drug's safety and efficacy. The safety and effectiveness of the generic are assured by showing that, among other things, the generic drug has the same active ingredients as the innovator. Because evidence presented to the agency demonstrates Premarin may have active ingredients in addition to those identified in the USP monograph, the agency cannot at this time approve an ANDA for a synthetic form of conjugated estrogens unless the active ingredients in Premarin are adequately identified and the ANDA demonstrates that the generic product contains the same ingredients.

**10. WHAT WILL HAPPEN TO THE USP MONOGRAPH FOR CONJUGATED ESTROGENS?**

CDER is considering making recommendations to the USP regarding the current scientific information about the composition of conjugated estrogens.

**11. WHY WAS THIS POSITION NOT DISCUSSED WITH AN ADVISORY COMMITTEE?**

The issue of the active ingredients in Premarin was discussed in 1989 with FDA's Fertility and Maternal Health Drugs Advisory Committee, in 1990 with an ad hoc subcommittee of this same committee, and in 1995 with this committee plus representation from FDA's Generic Drugs Advisory Committee and FDA's Endocrinologic and Metabolic Drugs Advisory Committee. Following each of these meetings, the Committee was unable to determine whether or not any individual component of Premarin or any combination of components other than estrone sulfate and equilin sulfate must be present in order for Premarin to achieve its established levels of efficacy and safety.

CDER's position regarding the approvability of generic conjugated estrogens at this time is consistent with the findings of the Advisory Committee; the position is based upon the fact that the active ingredients in Premarin have not yet been defined.

**12. WILL A GENERIC OF PREMARIN EVER BE APPROVED?**

Approval of a generic copy of Premarin would result in significant cost savings for American women, an outcome strongly supported by the FDA. Approval of a generic copy of Premarin will require an assurance that such copies contain the same active ingredients as Premarin. It is both feasible and desirable for the constituent active ingredients of Premarin to be characterized to this extent and Wyeth-Ayerst has committed to so characterize the active ingredients in Premarin.

**13. WHY HAS THIS ANNOUNCEMENT TAKEN SO LONG?**

Over the years, there has been considerable controversy about the required composition and testing of generic conjugated estrogens. The decision to approve a generic version of any drug, especially one in such widespread use, has profound medical and regulatory implications. The determination of bioequivalence upon which a generic approval is based must be supported by strong science. Newly available information about the composition of Premarin from modern analytical techniques coupled with the results from new clinical studies had to be thoroughly evaluated to be certain that a decision on whether or not to approve applications for generic Premarin was firmly grounded in sound, up-to-date science.

Fact-finding in the face of emerging new information adds significant time to the process. All available information has to be thoroughly considered to be as certain as current science allows that positions taken are in the

best interest of the public health.

**14. IS THERE CONSENSUS WITHIN THE FDA FOR THIS POSITION?**

Although support for CDER's approach has not been unanimous, the full range of views and evidence was thoroughly considered in reaching CDER's position.

**15. HAS THERE BEEN EXTERNAL PRESSURE (FROM WYETH-AYERST, CONGRESS, THE GENERIC MANUFACTURERS) TO INFLUENCE THIS POSITION?**

Issues with this level of public interest often stimulate interested parties to provide information to influence CDER. CDER considers all relevant information, regardless of its source, when considering important matters.

**16. COULD FDA APPROVE GENERIC COPIES OF PREMARIN MADE FROM THE PREGNANT MARES' URINE?**

Despite the fact that Premarin is not adequately characterized at this time, the Agency could approve generic copies of Premarin that originate from the same source material (pregnant mares' urine). This is because the reference listed drug is manufactured and controlled using these methods, and there could be confidence that generic copies using the same source materials and controlled in the same manner would have the same level of assurance that the same active ingredients are in the generic product as are in Premarin.

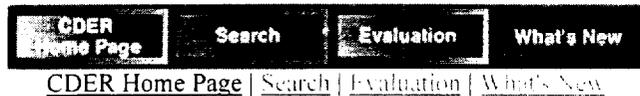
**17. ISN'T THE FDA CONCERNED ABOUT THE CRUELTY INFLICTED UPON PREGNANT MARES IN THE MAKING OF PREMARIN?**

A number of approved synthetic drug products, including piperazine estrone sulfate, micronized estradiol, and transdermal estradiol patches, are approved for the same indications as Premarin and are not derived from animal sources. In addition, FDA encourages the initiation of studies that will permit the scientific determination of the active ingredients in Premarin and allow potential approval of synthetic generic versions of the drug. Once Premarin has been sufficiently characterized, FDA is committed to the expeditious review and approval of synthetic generic conjugated estrogens with the same active ingredients as, bioequivalent to, and thus assured to be as safe and effective as, Premarin.

**18. DOES FDA INTEND TO ANSWER WYETH-AYERST'S CITIZEN PETITION, OR DOES TODAY'S ANNOUNCEMENT EFFECTIVELY ANSWER THE PETITION?**

Today's announcement provides CDER's current position on the approvability of applications for generic synthetic conjugated estrogens drug products. Along with the announcement, CDER has made public a detailed memorandum

regarding the approvability of a generic version of Premarin. CDER expects to receive comments on the announcement and underlying memorandum. If comments on the announcement and underlying memorandum are submitted to the Wyeth-Ayerst citizen petition docket, the agency will consider those comments in responding to the petition. The timing of FDA's petition response will depend, in part, on the volume of new comments and submissions received after the release of the announcement and memorandum.



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<http://www.fda.gov/cder/ceqa.htm>

