Memorandum

Date MAY 16 1997

From June Gibbs Brown
Inspector General

Subject Review of the Food and Drug Administration's Handling of Issues Related to Conjugated Estrogens (A-15-96-50002)

To Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration

The attached report provides the results of our review of the Food and Drug Administration's (FDA) handling of issues related to conjugated estrogens (Premarin), a commonly prescribed product for menopausal symptoms and the prevention and management of osteoporosis. This review was performed at the request of the Chairman, Subcommittee on Oversight and Investigations, House Committee on Commerce.

We were specifically asked to respond to questions regarding: whether unapproved formulations of Premarin are being marketed by its manufacturer, Wyeth-Ayerst; whether data exists showing that the currently marketed version of Premarin is safe and effective compared to an earlier version tested in the 1970's; the basis upon which FDA approved a new Premarin-based product called Prempro; and FDA's processing of a Wyeth-Ayerst citizen petition requesting the agency to recognize a third active ingredient in Premarin and not approve any generic versions lacking the third ingredient.

If you have any questions or comments regarding the issues discussed in this report, please call me or have your staff contact Joseph J. Green, Assistant Inspector General for Public Health Service Audits, at (301) 443-3582.

Attachment

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S HANDLING OF ISSUES RELATED TO CONJUGATED ESTROGENS

JUNE GIBBS BROWN
Inspector General

MAY 1997
A-15-96-50002

EXECUTIVE SUMMARY

BACKGROUND

The Food and Drug Administration (FDA) is the Federal agency responsible for approving applications to market new drugs, new indications for already marketed drugs, and generic versions of brand name drugs. Conjugated estrogens products represent a class of marketed drugs used primarily for the treatment of menopausal symptoms in women and for the prevention and management of osteoporosis, a crippling disease that causes thinning of the bone. Wyeth-Ayerst is a drug manufacturer that markets: (1) Premarin, approved in 1942, which is made from the urine of pregnant mares and is the Nation's only conjugated estrogens product; and (2) Prempro, approved in 1994, which combines Premarin and another hormone called progestin. At this time, there are no approved applications to market generic versions of these brand name drugs.

Once a drug is approved, drug manufacturers are required to obtain FDA's approval before adding or deleting an ingredient, or otherwise changing the composition of a drug product, other than deletion of an ingredient intended only to affect the color of the drug product. Current regulations require that when there is a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application, drug manufacturers are required to show that any reformulations are bioequivalent[1] to the approved product.

The FDA uses a process called the citizen petition to allow anyone--individuals or companies--to request the agency to make changes to its regulations. In November 1994, Wyeth-Ayerst submitted a citizen petition requesting FDA to: (1) recognize an ingredient of Premarin--delta 8,9 (dehydroestrone sulfate (DHES))--as an essential (but not an active[2]) ingredient in Premarin; and (2) not approve any generic version of Premarin that does not contain DHES. The firm amended its petition in December 1996 to request FDA to recognize DHES as an active ingredient. To date, FDA has not made a decision as to whether to approve Wyeth-Ayerst's citizen petition request. However, on May 5, 1997, FDA's Director, Center for Drug Evaluation and Research (CDER), announced that, because the active ingredients of Premarin have not been adequately defined, the agency could not at this time approve generic applications for synthetic versions of conjugated estrogens. The FDA had been reviewing two such applications since 1994 and 1995, respectively.

The House Committee on Commerce, Subcommittee on Oversight and Investigations, has raised concerns that Wyeth-Ayerst may have made misrepresentations in its submissions to

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[1] To show bioequivalence between reformulated drugs, there must not be a significant difference in the rate and extent to which the active ingredient of each product becomes available at the site of drug action.

[2] An active ingredient is any component that is intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease.

FDA regarding Premarin, and that FDA may have failed to adequately review such submissions. The Subcommittee requested the Office of Inspector General (OIG) in July 1996 to answer specific questions regarding: Premarin, another Wyeth-Ayerst product called Prempro, the citizen petition related to Premarin, and generic versions of Premarin.

OBJECTIVE

Our objective was to answer the Subcommittee's questions in the following three areas:

1. Premarin: The questions focused on possible unapproved reformulations; whether the reformulations were bioequivalent; and the basis on which FDA allowed the continued marketing of Premarin.

2. Prempro: The question focused on the basis on which Wyeth-Ayerst won approval for Prempro's use in the prevention and management of osteoporosis.

3. Wyeth-Ayerst's citizen petition regarding Premarin and generic versions of Premarin: The questions focused on FDA's examination of data and claims made in Wyeth-Ayerst's citizen petition and the agency's handling of brand name and generic versions of Premarin.

SUMMARY OF FINDINGS

Premarin: According to FDA, there have been no unapproved formulations of Premarin. Regarding the issue of bioequivalency among the formulations, however, we found that FDA does not have evidence demonstrating that the currently marketed formulation of Premarin is bioequivalent to the version tested for osteoporosis in the late 1970's. This is because no in vivo (i.e., in the living body) bioequivalence requirement was in effect for conjugated estrogens at that time. Concerned about lack of bioequivalency data and the continued safety and effectiveness of Premarin, FDA in 1993 directed Wyeth-Ayerst to conduct a new dose-ranging study of the drug. As of January 1997, 818 women, or about 30 percent of the total planned enrollment of 2,688, have entered into the multi-year study.

Prempro: The Premarin tablet formulation used in the combination drug Prempro (Premarin/medroxyprogesterone acetate) slightly differed from the marketed Premarin, but Wyeth-Ayerst submitted in vivo bioequivalence data to demonstrate that the new and currently marketed formulations were bioequivalent.

Citizen Petition and Generic Versions of Premarin: The FDA is in the process of reviewing the claims and data associated with Wyeth-Ayerst's citizen petition, which was submitted to the agency over 2 years ago. The FDA has thus far found deficiencies in the design of studies submitted to support Wyeth-Ayerst's claims, but no misrepresentations in data in the firm's studies have been identified. Regarding the Subcommittee's concern that FDA may have held generic drug firms to a higher standard than the brand-name maker of Premarin,

Wyeth-Ayerst, we noted that the agency was also concerned about possible differing standards in terms of bioequivalency requirements for the generic and brand name versions. However, upon further investigation, FDA determined there were no unapproved reformulations of the brand name Premarin that would have required Wyeth-Ayerst to submit additional bioequivalency data.

Beyond the Subcommittee's specific questions, we identified other concerns regarding the citizen petition process--namely that the process has been extended for an excessive period of time in the Wyeth-Ayerst case; and FDA does not have policies and procedures governing such an important process, one which can impact the marketability of generic versions of Premarin.

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INTRODUCTION

BACKGROUND

FDA ROLE AND ORGANIZATION

The FDA is the Federal agency responsible for approving applications to market new drugs, new indications for already marketed drugs, and generic versions of brand name drugs. Since 1962, sponsors have been required to demonstrate to FDA that their drug is both safe and effective. Prior to 1962, there was only the requirement to show the drug was safe.

Once a drug is approved, drug manufacturers are required to obtain FDA's approval before adding or deleting an ingredient, or otherwise changing the composition of a drug product, other than deletion of an ingredient intended only to affect the color of the drug product. Current regulations require that when there is a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application, drug manufacturers are required to show that any reformulations are bioequivalent to the approved product.

Various organizations within FDA are responsible for handling issues regarding brand name and generic drugs:

- The FDA's CDER is the organization that handles drug issues. One of CDER's chief responsibilities is reviewing new drug applications (NDAs) that sponsors submit to seek approval for marketing new drug products. Within CDER, 5 offices of drug evaluation oversee 15 divisions that review NDAs for new brand name prescription drugs. For conjugated estrogens, the Division of Metabolism and Endocrine Drug Products was responsible for handling Premarin until 1996 when responsibility was transferred to the newly formed Division of Reproductive and Urologic Drug Products.

- The CDER's Office of Generic Drugs (OGD) is responsible for processing applications from sponsors seeking to market generic versions of brand name drugs.

- The CDER's Office of Compliance, Division of Scientific Investigations, is responsible for directing and coordinating on-site inspections of sponsors and investigations of preclinical and clinical drug product studies.

- The FDA's Office of Regulatory Affairs (ORA) directs the agency's field staff which, among other duties, performs inspections of regulated firms. The ORA conducts routine inspections according to a pre-determined schedule; and for-cause inspections, which are requested for specific reasons. The ORA also oversees the implementation of the policy entitled, "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities," (also known as FDA's Fraud Policy), published in the Federal

Register in 1991 to address instances when misrepresentations are suspected in submissions to the agency.

To augment FDA's decisionmaking processes, the agency routinely uses advisory committees to provide scientific input to its product approval processes. To address various issues regarding conjugated estrogens, FDA has over the years convened the Obstetrics and Gynecology Advisory Committee, the Fertility and Maternal Health Drugs Advisory Committee, the Endocrinologic and Metabolic Drugs Advisory Committee, and the Generic Drugs Advisory Committee.

CONJUGATED ESTROGENS

Conjugated estrogens products represent a class of marketed drugs used primarily for the treatment of female menopausal symptoms, such as hot flashes, and for the prevention and management of osteoporosis, a crippling disease that causes thinning of the bone. Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They also contribute to the shaping of the skeleton.

Premarin, manufactured by Wyeth-Ayerst from the urine of pregnant mares, is the only brand of conjugated estrogens sold in the United States, with over 8 million women taking it daily. The FDA first approved Premarin in 1942 as safe for its intended use in the treatment of various menopausal symptoms; and in 1986, it deemed Premarin and the entire class of short-acting estrogens[3] as effective for the prevention and management of osteoporosis.

In 1994, FDA approved Wyeth-Ayerst's new drug application to market Prempro, a drug combining Premarin and another hormone--progestin. Studies have shown that the introduction of progestin lowers the incidence of endometrial cancer for the woman whose uterus is intact. Premarin continues to be prescribed for the woman who has had her uterus removed.

DRUG EFFICACY STUDY IMPLEMENTATION REVIEW PROCESS FOR DETERMINING EFFECTIVENESS OF PREMARIN FOR OSTEOPOROSIS

With the enactment of the 1962 Harris-Kefauver Amendments to the Federal Food, Drug, and Cosmetic Act, sponsors were required to demonstrate both safety and efficacy in order to market new drugs. For drugs approved between 1938 and 1962, when only the demonstration of safety was required, FDA contracted for retrospective Drug Efficacy Studies with the National Academy of Sciences/National Research Council. This action led to Drug Efficacy Study Implementation (DESI) panels to assess the efficacy of pre-1962 drugs in the marketplace. In 1972, based on a DESI review, FDA concluded that Premarin

[3] A short-acting estrogen is a drug or drug product which releases the estrogen relatively promptly after administration and which requires frequent dosing, ranging from daily to weekly.

was effective for certain indications related to menopause, and was "probably effective" for selected cases of osteoporosis. For the latter case, FDA required sponsors to submit substantial evidence of effectiveness or remove the indication from the product labeling within a certain period of time. Wyeth-Ayerst provided data to FDA in order to upgrade the osteoporosis indication; however, in 1976, the agency determined that the firm's data did not provide substantial evidence of effectiveness.

Based on published clinical study data of an estrogen product called mestranol, presented at the 1977 meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee and the 1978 meeting of FDA's Obstetrics and Gynecology Advisory Committee, members of both committees concluded that substantial evidence was available demonstrating that estrogens, including Premarin, effectively prevented post-menopausal bone loss. Both committees also recommended a dose equivalent to 0.625 mg. Premarin for osteoporosis management as the lowest dose to assure efficacy while minimizing the risk of endometrial cancer. The FDA accepted the new osteoporosis indication for the class of non-contraceptive short-acting estrogen drugs, which included Premarin, and required that the lowest effective dose of each estrogen product in the management of osteoporosis be rigorously delineated as the basis for approval of each product.

In April 1986, based on two dose-ranging clinical studies, FDA upgraded the effectiveness status of Premarin and other drugs in its class to "effective" for use in the prevention and management of osteoporosis in post-menopausal women. One of the studies, conducted by Robert Lindsay in the late 1970's and published in 1984 (hereafter referred to as the Lindsay study), has been considered the pivotal study demonstrating the lowest effective dose of Premarin for the prevention and management of osteoporosis.

GENERIC DRUGS

The Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417, dated September 24, 1984), also referred to as the Waxman-Hatch Act, amended the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(j)(2)A to require that generic drugs be shown to be bioequivalent to the appropriate brand name drug that has already been approved by FDA as safe and effective. By law, an applicant must demonstrate to FDA that the proposed generic drug is bioequivalent to the brand name drug, meaning that there is an absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action. The applicant must also demonstrate to FDA that the proposed generic drug is a pharmaceutical equivalent of the brand name drug in terms of identity, strength, quality, and purity.

From the mid-1970's to 1991, numerous generic versions of conjugated estrogens tablets were marketed in the United States. In February 1990, however, FDA proposed withdrawing approval of generic Premarin tablets applications due to a documented lack of bioequivalence (faster rate of absorption compared to brand name Premarin) and consequent concerns about safety and efficacy. Between March and May 1991, FDA withdrew approval

for all generic applications for conjugated estrogens tablets, and these generic products were withdrawn from the market. In 1994 and 1995, respectively, two sponsors submitted to FDA applications to market generic versions of conjugated estrogens based on synthetic ingredients. However, on May 5, 1997, the Director of CDER announced that, because the active ingredients of Premarin have not been adequately defined, the agency could not at this time approve generic applications for synthetic versions of conjugated estrogens.

CITIZEN PETITION PROCESS

Through the citizen petition process, FDA allows anyone--individuals or companies--to request the agency to make changes to its regulations. The citizen petition regulations cited at 21 C.F.R. Section 10.30, require FDA to furnish a response to each petitioner within 180 days of receipt of the petition. The response will either: (1) approve the petition; (2) deny the petition; or (3) provide a tentative response.

Wyeth-Ayerst is using the citizen petition process to request FDA to recognize an ingredient of Premarin as essential. Although FDA has always recognized two active ingredients in Premarin--sodium estrone sulfate and sodium equilin sulfate--Wyeth-Ayerst submitted a citizen petition to FDA in November 1994, requesting the agency to: (1) designate a component of Premarin--DHES--as an essential (but not an active) ingredient in Premarin; and (2) not approve any generic product which does not contain DHES. The firm amended its petition in December 1996 to request FDA to recognize DHES as an active ingredient. To date, FDA has not made a decision as to whether to approve Wyeth-Ayerst's petition request.

CONGRESSIONAL CONCERNS

The House Committee on Commerce, Subcommittee on Oversight and Investigations, has raised concerns that Wyeth-Ayerst may have made misrepresentations in its submissions to FDA regarding Premarin, and that FDA may have failed to adequately review such submissions. The Subcommittee requested OIG in July 1996 to answer specific questions regarding Premarin, another Wyeth-Ayerst product called Prempro, the citizen petition related to Premarin, and generic versions of Premarin.

OBJECTIVE, SCOPE, AND METHODOLOGY

The objective of our review was to answer specific questions about FDA's regulation of Wyeth-Ayerst's conjugated estrogens product, Premarin, posed by the Chairman, House Subcommittee on Oversight and Investigations, Committee on Commerce, in a July 11, 1996 letter to the Inspector General.

To answer these questions, we reviewed applicable laws, regulations, policies, and procedures pertaining to new drug applications, supplements, and amendments. We also reviewed FDA's regulation on citizen petitions and FDA's policy on "Fraud, Untrue

Statements of Material Facts, Bribery, and Illegal Gratuities," also known as the "FDA Fraud Policy."

We attended a briefing on conjugated estrogens presented by CDER focusing on: (1) an overview of conjugated estrogens; (2) historical review of the regulation of estrogen drug products by FDA; (3) estrogen chemistry; and (4) generic conjugated estrogens. We reviewed the NDA file for Premarin containing: data submitted by Wyeth-Ayerst, FDA's review of these data, correspondence between FDA and Wyeth-Ayerst, minutes of meetings between FDA and Wyeth-Ayerst representatives, minutes of FDA internal meetings, internal FDA correspondence, and other related documents.

We interviewed FDA staff responsible for reviewing data on Premarin as well as supervisory and management officials. We also obtained reports of inspections of Wyeth-Ayerst manufacturing facilities conducted by FDA staff. In addition, we reviewed citizen petitions filed by Wyeth-Ayerst with FDA pertaining to Premarin and various analyses and responses to these petitions. We did not review pending applications for generic versions of Premarin.

Our review was limited to addressing questions posed by the Subcommittee and thus did not include an overall assessment of the internal controls over FDA's procedures for processing new drug and generic drug applications and for handling citizen petitions. Further, our review did not include an evaluation of the scientific merits of decisions made regarding Premarin, Prempro, and related generic versions of these products. We provided FDA with a draft copy of this report, and incorporated its comments where appropriate.

Our review, performed during September 1996 through January 1997, was conducted in accordance with generally accepted government auditing standards.

RESULTS OF REVIEW

The following paragraphs present a brief summary of our findings in the areas covered by our review: Premarin, Prempro, the citizen petition, and generic versions of Premarin. Following the summaries is a more detailed discussion of each of these areas presented in a question-and-answer format.

Premarin: According to FDA, there have been no unapproved formulations of Premarin. Regarding the issue of bioequivalency among the formulations, however, we found that FDA does not have evidence demonstrating that the currently marketed formulation of Premarin is bioequivalent to the version tested for osteoporosis in the late 1970's. This is because no in vivo bioequivalence requirement was in effect for conjugated estrogens at that time. Concerned about lack of bioequivalency data and the continued safety and effectiveness of Premarin, FDA, in 1993, directed Wyeth-Ayerst to conduct a new dose-ranging study of the drug. As of January 1997, 818 women, or about 30 percent of the total planned enrollment, have entered into the multi-year study.

Prempro: The Premarin tablet formulation used in the combination drug Prempro (Premarin/medroxyprogesterone acetate) slightly differed from the marketed Premarin, but Wyeth-Ayerst submitted in vivo bioequivalence data to demonstrate that the new and currently marketed formulations were bioequivalent.

Citizen Petition and Generic Versions of Premarin: The FDA is in the process of reviewing the claims and data associated with Wyeth-Ayerst's citizen petition, which was submitted to the agency over 2 years ago. The FDA has thus far found deficiencies in the design of studies submitted to support Wyeth-Ayerst's claims, but no misrepresentations in data in the firm's studies have been identified. Regarding the Subcommittee's concern that FDA may have held generic drug firms to a higher standard than the brand-name maker of Premarin, Wyeth-Ayerst, we noted that the agency was also concerned about possible differing standards in terms of bioequivalency requirements for the generic and brand name versions. However, upon further investigation, FDA determined there were no unapproved reformulations of the brand name Premarin that would have required Wyeth-Ayerst to submit additional bioequivalency data.

Beyond the Subcommittee's specific questions, we identified other concerns regarding the citizen petition process--namely that the process has been extended for an excessive period of time for the Wyeth-Ayerst case; and FDA does not have policies and procedures governing such an important process, one which can impact the marketability of generic versions of Premarin.

PREMARIN

This section addresses the questions raised by the Subcommittee regarding possible unapproved reformulations; whether the reformulations were bioequivalent; and the basis on which FDA allowed the continued marketing of Premarin.

Question 1: Did reformulations of Premarin receive prior approval from FDA? Does FDA have data from Wyeth-Ayerst to support the changes in the Premarin formulation through the years?

We identified two reformulations--both received prior FDA approval and Wyeth-Ayerst submitted adequate data to support the reformulations.

We identified another "apparent" reformulation involving the Premarin shellac coating. Wyeth-Ayerst did not consider this to be a reformulation, and the firm was able to demonstrate to FDA why it was not a reformulation.

An FDA inspection conducted in September 1993 found there were no unapproved reformulations of Premarin; however, the agency did not document its inspection results.

Two Reformulations

Reformulation Involving Microcrystalline Cellulose

The first reformulation--which received prior FDA approval and was supported by adequate documentation required at the time--occurred in the mid-1970's when Wyeth-Ayerst automated its Premarin tablet coating process. To switch from a manual to an automated coating process, Wyeth-Ayerst replaced about nine coat filler ingredients used in the manual coating process with microcrystalline cellulose. Wyeth-Ayerst filed supplemental new drug applications for this reformulation with FDA on September 25, 1972, and September 6, 1974.

In response to an FDA telephone request, Wyeth-Ayerst, on February 25, 1975, filed in vitro (i.e., within a glass or artificial environment) disintegration data for 0.3, 0.625, 1.25, and 2.5 mg. tablet batches made by both the manual and automated coating process as well as in vitro dissolution data for batches made by both methods for the 1.25 mg. tablet strength. On the basis of this data, FDA permitted this reformulation on April 22, 1975.

Reformulation Involving Rubidium Bromide

Subsequent to the FDA September 1993 inspection of its facility, Wyeth-Ayerst reformulated Premarin by removing talc triturate containing rubidium bromide from the tablet and replacing it with an equal amount of lactose. To support this reformulation, Wyeth-Ayerst submitted the results of an in vivo bioequivalence study comparing the different formulations. The FDA, on December 23, 1994, found the study acceptable and approved the reformulation.

"Apparent" Reformulation: Shellac Coating

According to FDA, in approximately 1989 or 1990, Wyeth-Ayerst instituted a reduction in the amount of shellac content in the Premarin tablet. The FDA was concerned that this reduction may have affected the dissolution profile of the tablet and cause Premarin to be released faster in the human body. Wyeth-Ayerst did not view the changes made to the shellac to constitute a reformulation, and was able to demonstrate to FDA's satisfaction that there was no change to the drug product.

FDA On-Site Verification of Premarin Formulations

In 1991, FDA officials began raising concern as to whether there had been unapproved formulations of Premarin. To address this issue, in September 1993, CDER staff accompanied an ORA inspector to the Rouses Point, New York facility of Wyeth-Ayerst, where Premarin is manufactured. As a result of this for-cause inspection, FDA concluded that there appeared to be no unapproved formulations or manufacturing changes to Premarin. This conclusion was included in a written technical review of a supplement to Wyeth-

Ayerst's NDA for Premarin tablets. The FDA, however, could not provide us with a written report or other documentation to support this conclusion.

Even though this for-cause inspection appeared to partially resolve several years worth of serious concerns about the safety and effectiveness of Premarin, FDA did not have in its files a written report documenting the CDER staff's findings, nor any other documentation explaining why these concerns were dispelled. It also did not have a summary of the meeting held in October 1993 with CDER management to discuss these findings. The CDER staff who conducted the inspection informed us that other work precluded their preparing an inspection report and meeting summary.

Question 2: ***Are there data showing bioequivalence between the version of Premarin marketed today and the version tested in the Lindsay study, which examined the lowest effective dose for osteoporosis prevention?***

The FDA acknowledges that there are no bioequivalency data linking the version of Premarin marketed today with the one used in the Lindsay study conducted in the late 1970's. Furthermore, bioequivalency to the drug tested in the Lindsay study is not likely to ever be demonstrated, according to FDA, because of the inability of Wyeth-Ayerst to replicate the manual coating process of the Premarin formulation used over 20 years ago for the Lindsay study tablets.

At the time that Wyeth-Ayerst reformulated Premarin with microcrystalline cellulose, FDA did not require in vivo bioequivalence testing when drug manufacturers changed their product. Thus, FDA cannot know with certainty that the Premarin tablets marketed today are bioequivalent to the tablets used in the Lindsay study. However, as described below, scientific literature published over many years has shown that estrogen products, including the current version of Premarin, are effective in the prevention and management of osteoporosis.

Question 3: ***Given that there are no data linking the currently marketed Premarin product to the version used in the pivotal Lindsay study, what data has FDA used to justify its determination that Premarin is effective and safe for the treatment of osteoporosis? Why has the agency not rescinded Premarin's osteoporosis indication?***

The FDA has relied on the scientific literature regarding estrogens to justify that Premarin is effective for the prevention and management of osteoporosis. Numerous clinical studies published in the scientific literature since the pivotal studies were conducted in the 1970's continue to show that Premarin is effective in reducing bone mineral loss.

In terms of safety, the scientific literature suggests that use of estrogens, including Premarin, is associated with health risks. Numerous studies confirm the association of post-menopausal use of estrogens with an increased risk of endometrial cancer--a risk that appears dependent on duration of treatment and on the dose (i.e., the risk increases with higher doses and the

length of duration). In addition, recent studies, such as one whose results were published in the June 1995 issue of the New England Journal of Medicine, have shown that women who use estrogens are at greater risk than non-estrogens users for developing breast cancer. The literature also demonstrates that, because of the risks of developing endometrial cancer by using Premarin by itself, the drug should be taken only by the woman whose uterus is not intact. For the woman whose uterus is intact, the literature suggests that Premarin be taken with progestin to reduce the risks of developing endometrial cancer.

Another serious safety issue deals with the recommended dose of Premarin. Internal FDA documents indicate that in 1991, CDER officials, based on published studies, began to question whether the recommended dose of Premarin--0.625 mg.--was too high and might pose a health hazard in terms of endometrial and breast cancer for long-term users. In 1993, CDER officials considered withdrawing the osteoporosis indication. Their concerns focused on the lack of bioequivalency data between the currently marketed version of Premarin to the tablet used in the Lindsay study and the lowest effective dose of the drug.

The FDA decided not to withdraw the osteoporosis indication, but instead opted to rely on the published literature. At a meeting held in October 1993 between FDA and Wyeth-Ayerst, FDA agreed to accept a supplement to the NDA for the osteoporosis indication provided that the firm conduct a new dose-ranging study of Premarin. This supplement was based on published research showing that short-acting estrogens, including Premarin, were effective for the prevention and management of osteoporosis. While the published literature appears to have demonstrated the efficacy of Premarin for osteoporosis, it still remains to be proven whether a lower dose may be safer and just as effective for osteoporosis as the currently recommended dose.

Such information, however, will not be available until Wyeth-Ayerst completes its multi-year dose-ranging study. The new dose-ranging study was initiated in August 1995. As of January 1997, 818 women, or about 30 percent of the total planned enrollment of 2,688, have entered into the multi-year study. The target date for completion of the dose-ranging study will be approximately 2 years from the enrollment of the last study subject.

Question 4: Has FDA conducted validity assessments on Premarin following the discovery of different formulations?

The FDA did not conduct a validity assessment[4] on Premarin following the permitted reformulation in 1975, nor after the discovery of the apparent change in shellac content that occurred in the late 1980's. According to FDA, validity assessments are geared more towards verifying generic drug applications rather than reformulations of brand name drugs.

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[4] A validity assessment is a means to verify that drug applications adequately characterize the actual manufacturing of the drug product.

In 1993, FDA identified an apparent reduction in the shellac content of Premarin tablets; and in September 1993, initiated a for-cause inspection to: (1) determine whether the amount of shellac used for sealing tablet cores had an effect on the way the tablets dissolved; and (2) collect records to identify other possible unapproved reformulations. As a result, FDA determined that the shellac that was used at the time of the inspection did not affect the in vitro dissolution rate of Premarin tablets and that there were no other unapproved reformulations.

As noted above in Question #1, FDA was deficient in documenting the results of this for-cause inspection and a related staff meeting.

PREMPRO

This section responds to a question raised by the Subcommittee regarding Prempro, a recently marketed Wyeth-Ayerst product combining estrogen with progestin. This combination is designed to reduce the risks of endometrial cancer.

Question: If there is not a reference drug[5] for conjugated estrogens on the market, what data did Wyeth-Ayerst submit to FDA to win approval for the osteoporosis indication for Prempro, its recently approved combination product?

According to FDA, the reference drug used for Prempro was the currently marketed version of Premarin, except the Premarin used in Prempro does not include talc triturate and rubidium bromide. These ingredients were removed from the Premarin tablet and replaced by an equal amount of lactose. Because of this reformulation, FDA required that Wyeth-Ayerst conduct an in vivo study to show that the two formulations were bioequivalent. According to FDA, during 1994, the firm submitted a bioequivalency study that included data on 52 women, which demonstrated that the old and new formulations were bioequivalent. While the two most recent formulations have been shown to be bioequivalent, it must be noted, as we discussed above, that data does not exist linking these formulations to the Premarin used in the Lindsay study.

CITIZEN PETITION AND GENERIC VERSIONS OF PREMARIN

This section responds to questions raised by the Subcommittee about Wyeth-Ayerst's and FDA's handling of issues related to the citizen petitions and generic drug versions of Premarin:

[5] A reference drug is the FDA-approved drug upon which a drug applicant is basing its new drug product.

Question 1: Has FDA applied its fraud policy to examine the veracity of claims made by Wyeth-Ayerst in its citizen petition filed with FDA in November 1994, that "alleged but did not provide supportive data that DHES had some biological activity?"

The FDA has not invoked the fraud policy to analyze Wyeth-Ayerst's claims. According to a cognizant FDA official, the fraud policy is more directed to misrepresentation-of data in application submissions, rather than differing scientific opinions.

In terms of Wyeth-Ayerst's contention that DHES has some biological activity, and thus should be required to be included in generic versions, the firm has submitted to FDA clinical and pharmacokinetic study data that it believes supports this claim. The agency concluded that the clinical study was scientifically deficient for, among other things, not having a control group. The FDA's Division of Scientific Investigations has performed audits on data from the following two studies: (1) "A Pilot Study on the Clinical Effect of Delta 8,9, Dehydroestrone Sulfate Alone or in Combination with Estrone Sulfate;" and (2) "A Comparative Bioavailability Study of Premarin (0.625 mg.) and Estratab (0.625 mg.) in Healthy Post-Menopausal Females." Although the studies were found to be deficient, we are not aware of any misrepresentation in Wyeth-Ayerst's data provided to FDA regarding issues in its citizen petition.

Because the citizen petition has been under review for over 2 years by FDA, Wyeth-Ayerst has been able to provide FDA additional data to further substantiate its claims. Also, the agency has allowed the public, including drug companies seeking to develop generic versions of Premarin, to review and comment on Wyeth-Ayerst's claims. These mechanisms could serve as an additional method to identify the possibility of inaccurate data.

Question 2: Were generic drug applications in the 1980's and those that have been subsequently received held to an apparent higher standard than brand name Premarin?

An FDA official involved in conjugated estrogens issues has cited possible differing standards for generic versions of Premarin marketed prior to 1991 and the brand name (innovator) product. However, a review of the history related to bioequivalence testing for both generic versions and brand name Premarin does not support this supposition.

Generic versions of Premarin were required in 1986 to show in vivo bioequivalence to brand name Premarin; however such bioequivalence could not be established because the generic products released faster in the body than the brand name version. As a result, in 1991, FDA required the generic products to be removed from the market. In 1993, this FDA official acknowledged bioequivalency issues were also associated with Premarin in that there were no bioequivalency data linking suspected reformulations of the product. The FDA official stated for the record:

> "Ironically, the same bioequivalence questions first raised by Wyeth-Ayerst [regarding generic versions on the market in the 1980's] now cast doubt upon

the safety and efficacy of Premarin. It would be neither consistent nor ethical, however, for FDA to apply a more lenient standard to the innovator firm now than was applied to the generic sponsors in 1990-91, when bioequivalence issues are virtually identical."

In 1993, FDA followed up on possible unapproved reformulations, and determined there were none. Had such unapproved reformulations been identified, and FDA not required Wyeth-Ayerst to submit additional bioequivalence data, then one could conclude that FDA had indeed applied a more lenient standard to Wyeth-Ayerst than the firms that had previously marketed generic versions of Premarin. Given that there were no unapproved reformulations, we could not substantiate the Subcommittee's concern that there were differing standards applied in this case.

Questions have been raised regarding the fast-releasing aspects of the drug because Wyeth-Ayerst, from 1967 to 1990, marketed in Canada a fast-releasing Premarin tablet that was similar to the generic versions marketed in the U.S. prior to 1991. However, according to FDA, Wyeth-Ayerst's fast-releasing product was not sold in the U.S. and FDA does not have regulatory oversight in a foreign country.

Regarding the generic versions currently being reviewed by FDA, we have not reviewed these pending applications, and thus we have no indications that they are being held to a higher standard than brand name Premarin.

Other Concerns about the
Citizen Petition Process

As a result of our review, we identified two significant concerns regarding the citizen petition process for the Premarin issue. First, in the Wyeth-Ayerst case, it appears that FDA has allowed the process to extend for an unacceptably long period of time--over 2 years. The regulations cited at 21 C.F.R. Section 10.30, require FDA to furnish a response to each petitioner within 180 days of receipt of the petition. The response will either: (1) approve the petition; (2) deny the petition; or (3) provide a tentative response. In this case, at the 180-day point, FDA informed Wyeth-Ayerst that the petition was "still under consideration."

In July 1995, FDA convened the Fertility and Maternal Health Drugs Advisory Committee to discuss the clinical effects of conjugated estrogens. This committee determined that there were insufficient data to assess whether or not DHES or any component must be present in generic versions of Premarin to achieve clinical safety and efficacy. The agency also established an ad hoc conjugated estrogens working group comprising scientific, legal, and policy experts to address the issues raised in the petition. Cognizant officials have indicated to us that the petition process has been extended to allow for the submission of public comments and analysis of data. Such data continued to be submitted to the agency up until December 1996. In December 1996, the firm amended its original petition to request that DHES be considered an "active" ingredient in Premarin.

Our second concern focuses on the absence of written policies and procedures for FDA's handling of citizen petitions. Such policies and procedures, we believe, are essential for any type of administrative process that can significantly impact the industries under FDA's regulatory purview. Although FDA has yet to decide whether it will approve Wyeth-Ayerst's citizen petition request, the Director of CDER announced on May 5, 1997, that the agency could not currently approve generic applications for synthetic versions of conjugated estrogens because the active ingredients of Premarin have not been adequately defined. According to CDER officials, CDER began developing a citizen petition policy several months ago and expects to complete it soon.

CONCLUSIONS

Premarin

The Subcommittee has raised serious questions regarding the safety and efficacy of Premarin--an important drug product used daily by millions of women. Regarding the formulations of Premarin, a September 1993 for-cause inspection confirmed there have been no unapproved reformulations of the drug product; however, FDA could not furnish documentation of its inspection results nor any other documentation explaining why its concerns about the drug's formulations were dispelled.

In terms of bioequivalency, there is no data link between the Premarin product tested in the late 1970's during a pivotal osteoporosis study and the product that is currently marketed. The FDA has relied on published data demonstrating Premarin's effectiveness for the prevention and management of osteoporosis, but has also raised concerns about the absence of bioequivalency data and the possibility that the dose of Premarin may be too high. To address these concerns, FDA directed Wyeth-Ayerst in October 1993 to conduct a new dose-ranging study of the drug. Until a new study is completed, the agency is relying on published data to demonstrate that Premarin is effective for osteoporosis.

Prempro

In terms of the recent Wyeth-Ayerst product, Prempro, the firm used the marketed version of Premarin as a reference drug in the new drug application, except the Premarin used in Prempro does not include talc triturate and rubidium bromide. These ingredients were removed from the Premarin tablet and replaced by an equal amount of lactose. Wyeth-Ayerst was able to demonstrate to FDA through in vivo testing that the two formulations were bioequivalent.

Citizen Petition Process and Generic Versions of Premarin

In terms of the Subcommittee's concern about possible fraudulent claims made by Wyeth-Ayerst in the citizen petition process, it appears that FDA has--and is using--appropriate

methods for identifying inaccuracies in the firm's data submissions. We did not identify instances where Wyeth-Ayerst received preferential treatment from FDA over generic drug sponsors. Our concerns with the citizen petition process focus on the length of time it has taken FDA to receive and analyze pertinent data in the Wyeth-Ayerst case and the absence of agency policies and procedures for handling such petitions.