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CITIZEN PETITION

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MAY 21 1998

Petitioner: Arnold & Porter for Wyeth-Ayerst

Docket Number: 98P-0311/CP1

Topic: NDAs for Synthetic Conjugated Estrogens

Date Submitted: 5/12/98

Date Received RPS: 5/13/98

RPS Lead: Carol Drew

Summary:

Requests that FDA, in review of NDA's for 5-estrogen synthetic products: 1. Require clinical studies to determine safety and effectiveness and not allow reference to clinical studies of other estrogens; 2. Revoke current USP monographs for conjugated estrogens and conjugated estrogen tablets; 3. Not allow "conjugated estrogens" in naming products; and 4. Require any such approved products to prominently disclose in labeling, sale and promotional materials that they are not equivalent to or substitutable for Premarin.

STATUS OF DOCUMENT:

Incoming Draft Response Final Response

ACTION REQUESTED:

ACTION REQUESTED:

ADDRESSEES	FXI Only	Review & Comment by (May 30)	Final Clearance by (date)	ADDRESSEES	FXI Only	Review & Comment by (May 30)	Final Clearance by (date)
J. Woodcock	X			R. Temple			
M. Lumpkin				J. Bilstad	X		
R. Williams	X			N. Weintraub			
S. Gray				N. Reuter			
D. Henderson				A. Wion	X		
D. Sporn	X			L. Rarick	X		
P. Botstein							
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Responsibility for this petition in CDER is assigned to the Regulatory Policy Staff (HFD-7) (RPS). Comments concerning the petition should be forwarded to the RPS lead. If your office wishes to draft the actual response to the petitioner, first contact RPS so that efforts can be coordinated. The RPS lead can be reached at phone: (301)594-2041; fax: (301)627-5562.

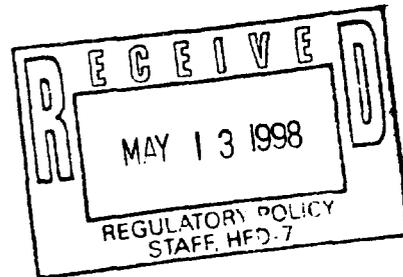
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May 12, 1998

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857



Citizen Petition Re: New Drug
Applications for Mixtures of Estrogens

Dear Sir or Madam:

We submit this petition on behalf of our client, Wyeth-Ayerst Laboratories, Division of American Home Products Corporation ("Wyeth-Ayerst"). Wyeth-Ayerst is the manufacturer and marketer of Premarin® (conjugated estrogens) tablets.

Background

Premarin is a multi-component, naturally derived product whose active ingredient is composed of conjugated estrogens and other steroidal and non-steroidal ingredients. The Center for Drug Evaluation and Research ("CDER" or "Center") has, during recent years, focused on the question whether conjugated estrogens could be defined properly as a product that needs to contain only five or six of those estrogens and no other steroidal components. Ultimately, the Center correctly concluded that it could not approve synthetic products containing only five or six estrogens as generic versions of Premarin. The Center's decision was based on its recognition that emerging scientific evidence indicates that different estrogens have different effects on the body. Accordingly, it could not be established that the synthetic mixtures of a limited number of estrogens would have the same safety and efficacy as Premarin, whose steroidal composition had not been fully characterized. [REDACTED] 1997 memorandum from Director, Center for Drug Evaluation and Research, to Director, Office of Generic Drugs).

This decision rejected arguments made by two generic drug manufacturers, Duramed Pharmaceuticals, Inc. ("Duramed") and Barr Laboratories, Inc. ("Barr"), who had each sought approval of abbreviated new drug applications ("ANDAs") for products containing only five estrogens. Duramed and Barr had argued that such products were

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suitable generic equivalents to Premarin. Duramed has announced that it has now filed a new drug application ("NDA") for the five-ingredient product, seeking its approval as estrogen replacement therapy in treating hot flashes and other vasomotor symptoms in post-menopausal women. See Exhibit B (Duramed Press Release, March 30, 1998). Press reports also indicate that Barr has agreed with Warner-Chilcott for that company to submit an NDA for the Barr five-estrogen product, presumably for similar indications. See E.D.C. Reports, The Pink Sheet, Oct. 1, 1997.

Wyeth-Ayerst is very concerned that Duramed and Barr by using this NDA route are seeking simply to make an end-run around CDER's decision of May 5, 1997. As noted below:

- The five-estrogen mixtures in issue were originally developed solely for the purpose of establishing a purported equivalence to Premarin which, as noted, CDER did not accept. The selection of this particular mixture to treat vasomotor symptoms has no apparent rationale other than to salvage the original formulation and get it on the market for use in estrogen replacement therapy.
- Neither Duramed nor Barr has receded from their widely publicized position that these five-estrogen products are equivalent to, and can be substituted for, Premarin. There is no indication that these companies will curtail dissemination of such views if they are permitted to market these products. Indeed, in letters recently sent to interested women's groups, Duramed expressly represents that its unapproved product, which it describes as "not made from pregnant horse urine," a clear reference to Premarin, "will provide an economic alternate estrogen replacement therapy to those postmenopausal women who prefer a synthetic choice." Exhibit C (April 9, 1998 letter from E. Thomas Arington to Betty Williams).
- The probability of public confusion with Premarin is further increased if these products are labeled as "Conjugated Estrogens, USP," something that is clearly anticipated by their manufacturers. See *id.* (Duramed reference to its product as "conjugated estrogens").

Wyeth-Ayerst submits that, given these circumstances, approval of the NDAs for these products is likely to lead to their use as substitutes for Premarin not only for vasomotor symptoms but also in long-term estrogen replacement therapy including treatment of osteoporosis. To protect the public and to prevent consumer deception, FDA 1) must assure that the Duramed and Barr products are safe for chronic use as well as in

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acute treatment of vasomotor symptoms before they are permitted to be marketed and 2) must take appropriate steps to assure that these products if approved will not be marketed as conjugated estrogens and as substitutable for Premarin.

A. Actions Requested

1. We ask that FDA, in its review of new drug applications for these mixtures of estrogenic components, make its determination as to whether the products meet the requirements of Section 505 of the Act relating to safety and effectiveness by applying the same strict standards it applies to all other new chemical entities. In that regard, we ask that FDA recognize that the applicants cannot satisfy their responsibility under Section 505(b) to demonstrate the safety and effectiveness of these mixtures of estrogenic components by relying on animal and human clinical studies of other estrogens such as estrone, equilin, or conjugated estrogens, because studies of any single estrogen or combination of estrogens do not necessarily support the safety and effectiveness of any other single estrogen or combination of estrogens. We also request that FDA recognize that these products will inevitably be used for chronic estrogen replacement therapy as well as for acute vasomotor symptoms.
2. We ask that FDA move promptly to seek revocation of the current United States Pharmacopeia ("USP") monograph for conjugated estrogens, as that monograph is inaccurate and inconsistent with the May 5, 1997 Center decision on the composition of conjugated estrogens. An accurate monograph can be substituted once the characterization process for Premarin has been completed. We also ask that FDA seek revocation of the USP monograph for conjugated estrogens tablets.
3. We ask that FDA recognize that the mixture of estrogenic ingredients in the Duramed and Barr products is materially different from Premarin conjugated estrogens and that those products therefore should not be called "conjugated estrogens," nor should "conjugated estrogens" be any part of their common or usual (chemical) name. If NDA approval of those products is permitted, a different and clearly distinctive chemical name should be chosen for them.
4. We ask that, if FDA does approve the Duramed or Barr new drug applications or any other application for a mixture of some but not all the active steroids in Premarin, the marketers of such products be required to disclose prominently in all labeling and promotional and sales materials (including price sheets and

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any materials supplied to third parties) the fact that these drugs are not equivalent to and should not be substituted for Premarin.

B. Statement of Grounds

- 1. Because the Composition of These Estrogen Products Differs from That of Previously Marketed Products, The Proposed Products Should Not Be Approved in the Absence of Full Compliance with NDA Safety Data Requirements.**

The combination of estrogens in the Duramed and Barr products is, as CDER has determined, not the same as Premarin. It is simply the formulation that they had put together to try to obtain ANDA approval based on an assessment, now found by CDER to be incorrect, of the relevant estrogens in Premarin. Such products must meet FDA requirements substantiating their safety as well as efficacy on the basis of their own particular composition. Yet the announcement by Duramed of its NDA makes no reference to performance of the type of safety studies that would normally be required for the approval of a new drug. Moreover, the time in which that NDA has apparently been prepared is so short as to suggest that such safety studies have not been completed.

- a. Safety data with Premarin or other estrogen drugs used in estrogen replacement therapy do not demonstrate the safety of the proposed products under the requirements of Section 505.**

The fact that the estrogens used in these products are some but not all of the active components of Premarin does not show the five-estrogen mixture to be safe. Premarin contains a number of steroidal components beyond those found in the Duramed and Barr mixtures. Some of the steroidal components of Premarin may have a protective effect or may compete as antiestrogens for estrogen receptors with estrogens that could otherwise cause adverse effects. The potential toxicity associated with the limited number of synthetic estrogens in the Duramed and Barr products may thus differ from that of Premarin in unknown ways. The issues are complex. See, for example, CDER's analysis:

Stimulatory effects [of Premarin components] on liver proteins may affect drug safety. In addition, as discussed in the OCPB Report, levels of circulating unconjugated estrogens may be affected by binding to plasma proteins, particularly sex hormone binding globulin (SHBG). Stimulation of SHBG could alter drug availability. Available data suggest that certain Premarin components differ in the ability to stimulate SHBG.

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Exhibit A (CDER May 5, 1997 memorandum) at 19 (footnote omitted). Omission of a number of the estrogens and other steroids found in Premarin could have safety effects that can not be predicted in the absence of data addressing these issues.

Premarin has been shown to present a favorable risk-benefit ratio. That does not mean, however, that any subset of the steroids in Premarin can be presumed to be safe. See, e.g., Exhibit A (CDER May 5, 1997 memo) at 10: "the clinical tests, on which the findings of the safety and efficacy of Premarin were based, were performed on the entire mixture, not on individual components."

Moreover, as CDER's analysis reflects, CDER rejected the formerly held belief "that all estrogens were similar in their pharmacologic actions on the body, i.e., 'an estrogen is an estrogen'." *Id.* at 8. Instead, it noted:

Emerging scientific evidence demonstrates that all estrogens do not exert their effects in a uniform manner with respect to different target tissues. These differential effects may be due to variable pharmacokinetics, tissue metabolism, tissue-specific receptor factors, or additional reasons.

Id. at 9 (references omitted).

Hence, Duramed and Barr cannot claim that safety data, literature references, FDA approvals, or clinical experiences associated with other estrogen drugs containing different estrogen compositions are acceptable to show the safety of their products for their intended uses. To rely on such information, these companies would have to show that the compositional differences in components between such drugs and the five-estrogen products in issue would not make such extrapolations inappropriate. There is no basis on which they could make that showing. It is simply not known whether the differences between the components in the Duramed and Barr mixtures and those in previously approved estrogen products would cause the Duramed and Barr products to have a significantly different safety profile than the approved estrogen products.¹

¹ Certainly, as NDA applicants, Duramed and Barr bear the burden of proving that their products are safe and effective. Cf. 21 C.F.R. 12.87(d).

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b. The Duramed and Barr products should undergo standard safety testing applicable to new drugs.

At a very minimum, we suggest that approval of any novel mixture of estrogens should require the submission of safety information in accordance with well-recognized FDA and other regulatory requirements. To our knowledge, such studies have not been performed with most of the individual estrogens in the proposed mixture. It seems highly unlikely that they have been performed on the specific mixture of those components contained in the Duramed and Barr products. Adherence to these requirements is particularly justified in the case of new compositions of estrogen products.

Given the current state of knowledge relating to differences in properties of various estrogens, these requirements should apply even if it could be assumed that the products would be limited to short-term use. But here, the likelihood of longer use is very real. While the acute menopausal symptoms for which these products would be labeled may be of only short duration in some women, they can last much longer in many others. Moreover, it is predictable that these drugs will also be used inappropriately for the chronic indications of estrogen replacement therapy, and indeed that would have been the explicit consequence of the ANDA approval their sponsors originally sought. Both manufacturers have been publicly quoted as believing their products are suitable for use for all of Premarin's indications. See pp. 9-10, *infra*.

It is inevitable that the Duramed and Barr products will be used in chronic estrogen replacement therapy by many women even though these drugs are indicated only for vasomotor symptoms. Premarin has been shown to be safe for such chronic use. There is no basis to assume similar safety for the novel mixture in the Duramed and Barr products. Indeed, the only argument supporting such a conclusion—that “an estrogen is an estrogen”—has been explicitly rejected by CDER. Given these market realities, there is no justification to dispense with the type of testing generally considered necessary for a chronically administered drug.

To conform to Agency and international regulatory standards, the NDAs should thus include as part of their safety substantiation clinical studies that are sufficient to demonstrate long-term clinical safety. For example, ICH Guidelines require that drugs intended for long-term treatment of non-life threatening indications be assessed in a prospective study involving at least 100 patients with a minimum of a one-year exposure to support a determination of safety. See Exhibit D (ICH, Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-

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term Treatment of Non-Life-Threatening Conditions, at 3 (March 1995)).² Failure to require such testing of the Duramed and Barr products because they would be labeled only for acute menopausal symptoms would require turning a blind eye to the foreseeable, if not inevitable, results of market forces.

2. FDA Should Promptly Seek Revocation of the Current United States Pharmacopeia Monographs for Conjugated Estrogens.

The original USP monographs for conjugated estrogens (bulk substance and tablets) were intended to describe Premarin, and for years were thought to do so. As the FDA has found, the current monographs, which describe a product containing only five of the estrogens in Premarin, were based on inadequate data and are inaccurate. They do not accurately describe Premarin and thus do not describe conjugated estrogens. They do, on the other hand, describe, and thus inappropriately validate, the Duramed and Barr products. They also foster the inappropriate inference that the Duramed and Barr products and Premarin are the same.

In public documents explaining its decision not to grant approvals of the ANDAs for the Duramed and Barr products, CDER explained that

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.

Exhibit E (Center for Drug Evaluation and Research, "Synthetic Conjugated Estrogens: May 5, 1997 Questions and Answers") at 3. Accordingly, it stated that:

² FDA has itself published detailed guidance on the type of preclinical and clinical studies that are necessary for a drug intended for prevention or treatment of osteoporosis. FDA, *Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis* (April, 1994). In light of the high likelihood that these drugs will be used for treatment of osteoporosis, FDA might reasonably conclude that such testing is necessary for them before they are approved.

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

Id.

Wyeth-Ayerst agrees that the USP monograph for the bulk substance does not accurately describe conjugated estrogens.³ There is not yet sufficient information available to prepare a new monograph that accurately reflects all of the active components of conjugated estrogens as contained in Premarin. Wyeth-Ayerst thus urges that FDA formally request that the United States Pharmacopeia promptly withdraw the current monograph for conjugated estrogens.

Not only is this monograph inaccurate, but its continuing presence creates the potential for significant confusion should FDA approve new drug applications for products containing only the five estrogens required by the monograph. Thus, its presence raises the potential that these products could be characterized as "conjugated estrogens USP," the same designation used by Premarin, which would inevitably blur the potentially important differences between these drugs and Premarin. Wyeth-Ayerst also urges FDA to seek withdrawal of the conjugated estrogens tablet monograph because, like the substance monograph, it fails to describe Premarin tablets as well as permits incorrect inferences to be drawn as to similarities between Premarin tablets and the Duramed and Barr products.

3. The Duramed and Barr Products Should Not Be Called "Conjugated Estrogens."

As FDA concluded in refusing to approve ANDAs for the Duramed and Barr products, those products are not the same as, and do not have the same active ingredient as, Premarin. Certainly, Premarin is conjugated estrogens and has been marketed under that name throughout its more than half a century of existence. Because the Duramed and Barr products are chemically and compositionally different from Premarin, they must bear a different common and usual (chemical) name in order to avoid confusion.

³ While Premarin "complies" with the monograph, that monograph does not specify all of the components of Premarin's active ingredient.

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FDA has the statutory authority to designate an official name for any drug product. Federal Food, Drug, and Cosmetic Act Section 508. While FDA does not frequently exercise that authority, it can do so in appropriate circumstances. In any case, the designation of an appropriate non-proprietary name for a drug is a condition precedent for approval of a new drug application. See, e.g., 21 C.F.R. 299.4(d).

As a general proposition, FDA has stated its agreement with the "Guiding Principles for Coining U.S. Adopted Names for Drugs," published in USAN and the USP Dictionary of Drug Names (now called the USP Dictionary of USAN and International Drug Names), 21 C.F.R. 299.4(d). One such guiding principle is that: "A name should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor misleading," USP Dictionary of USAN and International Drug Names, page 867 (1998). Thus, for example, the name "synthetic conjugated estrogens," which clearly suggests that the product is the same as conjugated estrogens, except for being synthetically produced, would be inappropriate. Under no circumstances should the term "conjugated" be used in conjunction with "estrogens." A name such as "synthetic sulfated estrogen mixture" would be appropriately descriptive yet distinct from conjugated estrogens.

The new name for the combination of estrogens for which Duramed and Barr seek approval may thus be adopted in the process of NDA approval, if there is to be an approval, or may be established by FDA pursuant to its authority under Section 508. In either case, it will be important, to avoid confusion, that the established name be clearly distinct from conjugated estrogens.

4. Any NDA Approval Must Be Conditioned Upon Clear Disclosures, in All Labeling and Promotion, That the NDA Products Are Not Equivalent to and Should Not Be Substituted for Premarin.

Duramed and Barr have each been very vocal about their position that their five-ingredient estrogenic products are the same as and are substitutable for Premarin conjugated estrogens. They have very publicly dismissed the FDA's painstaking scientific analysis leading to the contrary conclusion as being "politically motivated." Thus, Bruce Downey, President of Barr, characterized the FDA's careful scientific ruling as "the triumph of politics over science." See Exhibit F (The Cincinnati Enquirer, May 6, 1997). This statement was described in that report as "[e]choing a refrain used by Duramed throughout the FDA review." Id.

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Duramed and Barr are of course entitled to state their beliefs on the issue of the identity of their products to Premarin in whatever intemperate and disrespectful terms they choose, so long as they are not planning on marketing a product whose sales would benefit from such misleading statements. If the Duramed and Barr products are approved, they should be approved only as yet another estrogen product for menopausal symptoms, not as generic versions of conjugated estrogens or as otherwise substitutable for Premarin.

The arguments that the generic manufacturers have made on this issue to date are directly relevant to Wyeth-Ayerst's request concerning the marketing of any Duramed or Barr product approved under an NDA in two important respects: First, both manufacturers have already made numerous public statements concerning the similarity of these products to Premarin that many physicians and other customers will have heard and will understand to be applicable to the Duramed and Barr products. Second, the companies' apparently strongly held beliefs provide a good predictor of what they may be expected to say, in one context or another, if they obtain NDA approval. There is, after all, a limited market for one more novel combination of estrogens, while there is a potentially much larger market for a product that can be marketed as substitutable for or interchangeable with Premarin. Duramed has, in fact, already begun to refer to its unapproved product in communications to interested women's groups as a synthetic form of Premarin. See, e.g., Exhibit C (April 9, 1998 letter from E. Thomas Arington to Betty Williams) in which Duramed's President notes that the Duramed product, which he describes as "synthetic conjugated estrogens tablets," is "not made from pregnant horse urine" and suggests that it "will provide an economic alternate estrogen replacement therapy to those postmenopausal women who prefer a synthetic choice."

In this context, Wyeth-Ayerst believes that any marketing of such a product must, in order not to be misleading, be accompanied by clear statements in all labeling and promotion that this product is not equivalent to and should not be substituted for Premarin.⁴ Anything less will result in the type of substitution that FDA has correctly

⁴ FDA certainly has the authority to require, in appropriate circumstances, labeling references to the differences between drugs that might be substituted for each other. See, for example, the prominent warnings that appear in the labeling of Lilly insulin derived from recombinant DNA:

This Lilly insulin product differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because

[Footnote is continued on next page]

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concluded may put American women at risk.⁵ Certainly, at a minimum, all introductory promotional materials and labeling must contain such information.

5. Summary and Conclusion

For all the reasons discussed above, Wyeth-Ayerst believes that no NDA approval for a mixture of five of the estrogens found in Premarin is appropriate in the absence of safety testing of that mixture of the type required for any new chemical entity. If such an approval is to be granted, however, effective actions, including the revocation of the United States Pharmacopeia monographs for conjugated estrogens, the use of a different common and usual name, and restrictions on promotion of such products that implies equivalence to Premarin, should be undertaken promptly to prevent the improper substitution of the five-estrogen product for Premarin.

[Footnote is continued from previous page]

of its unique manufacturing process. Any change of insulin should be made cautiously and under medical supervision. . . .

Humulin® L, Information for Patient, Physicians' Desk Reference (52nd ed. 1998) at 1467.

See, also, product information for Roche Laboratories' Roferon-A, id. at 2492:

Patients should be cautioned not to change brands of Interferon without medical consultation, as a change in dosage may result.

⁵ It may be argued that Wyeth-Ayerst's request in this regard is premature. As a practical matter, however, if there is an approval of an NDA for either the Barr or Duramed product and the company is able to launch to its accounts with the assertion, implicit or otherwise, that the product is, as they have always maintained, equivalent to Premarin, corrective action thereafter will be far too late to be effective.

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C. Environmental Impact

The relief requested by this petition would result in the refusal to approve NDAs (thus not changing the status quo) or the imposition of conditions of marketing on any five-estrogen product approved by FDA. Because the grant of the petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. 25.31(a) (62 Fed. Reg. 40570, 40594 (July 29, 1997)).

D. Economic Impact

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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A

MEMORANDUM



**DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: May 5, 1997
FROM: Director, Center for Drug Evaluation and Research
SUBJECT: Approvability of a Synthetic Generic Version of Premarin
TO: Douglas L. Sporn
Director, Office of Generic Drugs

I. Introduction

This memorandum transmits the Center for Drug Evaluation and Research's (CDER) position on the circumstances under which an abbreviated new drug application (ANDA) for a synthetic version of Premarin could be approved at this time. The Center's conclusion is that because the reference listed drug Premarin is not adequately characterized at this time, the active ingredients of Premarin cannot now be definitively identified. Until the active ingredients are sufficiently defined, a synthetic generic version of Premarin cannot be approved. The legal and scientific rationale for this conclusion is described below.

Any synthetic generic conjugated estrogens application based on Premarin as the reference listed drug is not to be approved until the active ingredients of Premarin have been sufficiently well defined to permit an ANDA applicant to establish that a synthetic generic form of Premarin has the same active ingredients as Premarin. In addition, I am requesting that the bioequivalence guidance for conjugated estrogens be examined to determine whether it should be revised in view of this position.

II. Legal Requirements for Approval of an ANDA

Under section 505(j)(2)(A)(ii)(II) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), 21 U.S.C. § 355(j)(2)(A)(ii)(II), an abbreviated new drug application (ANDA) that refers to a listed drug with more than one active ingredient must contain, among other things, "information to show that the active ingredients of the new drug are the same as those of the listed drug..." Section 505(j)(3)(C)(ii) of the Act, 21 U.S.C. § 355(j)(3)(C)(ii), requires that the secretary shall approve

such an ANDA unless the Secretary finds, among other things, that "information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug...."

The implementing regulations provide that an ANDA not based on an approved suitability petition must provide information to show, among other things, that the active ingredients of the proposed and the reference listed drugs are the same (21 C.F.R. § 314.94 (a)(5)). FDA will refuse to approve an ANDA if "information submitted with the abbreviated new drug application is insufficient to show that the active ingredients are the same as the active ingredients of the reference listed drug" (21 C.F.R. § 314.127(a)(3)(ii)). The term "same as" means identical in active ingredient(s).¹ (21 C.F.R. § 314.92(a)(1))

The Agency has defined the term "active ingredient," as follows:

any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. (21 C.F.R. §§ 60.3(b)(2), 210.3(b)(7))

In the context of ANDA approvals, a generic product with the same active ingredients as the reference listed drug that is shown to be bioequivalent is approved without independent effectiveness data.* To meet the definition of an active ingredient in this context, a component must be intended to furnish sufficient pharmacological activity, or other direct effect, to have some therapeutic effect (i.e., to diagnose, cure, mitigate, treat, or prevent disease, or to affect the structure or function of the body). Thus, an active ingredient performs a drug's therapeutic functions. The definition of "pharmaceutical equivalents" in 21 C.F.R. § 320.1(c) is consistent with this definition of active ingredient in that it focuses on the therapeutic moiety:

Pharmaceutical equivalents means drug products that contain identical amounts of the identical active drug ingredients, i.e., the same salt or ester of the same therapeutic moiety...that meet

*In enacting the Drug Price Competition and Patent Term Restoration Act of 1984, Congress intended that no safety or effectiveness data beyond that developed by the innovator company be needed to support approval of the generic product. (See H.R. Rep. No. 857 (Part I), 98th Cong. 2d Sess. 14, 16-17 (1984)). The interpretation of the active ingredient definition in this memorandum is intended solely as applied to ANDA approval.

identical compendial or other applicable standards of identity, strength, quality, and purity, disintegration times and/or dissolution rates.

Consequently, not all components that "furnish pharmacological activity or other direct effect" meet the definition of an active ingredient. A component may be considered an active ingredient only if it provides a clinically meaningful contribution to the therapeutic effect of the drug. A subjective intent for a component to have such effect will not suffice in the absence of objective evidence of a clinically meaningful contribution. (See 21 C.F.R. § 201.128; intended use refers to objective intent.)

In most cases, it will be clear what components of a drug make clinically meaningful contributions to the drug's therapeutic effects and, therefore, are the drug's active ingredients. However, where the Agency has determined there is sufficient evidence that a component in the reference listed drug may make a clinically meaningful contribution to the therapeutic effect, FDA cannot approve a synthetic generic drug that does not include such component until it has been determined whether the component makes such a contribution.

III. Regulatory History of Conjugated Estrogens

FDA first permitted a new drug application for Premarin (conjugated estrogens tablets made from pregnant mare's urine) to become effective in 1942 under the new drug provisions of the 1938 FD&C Act, Pub. L. 75-717, 52 Stat. 1040, based on chemistry, manufacturing, and controls information acceptable at that time and a showing, from reports of clinical investigations, that the drug product was safe for its intended use in the treatment of menopausal symptoms and related conditions. The product was known at that time to contain estrone and equilin, and it was known that additional estrogens were present in smaller amounts. The tablet strengths and estrogenic potencies of Premarin tablets were controlled using a colorimetric assay and a rat bioassay, respectively, with estrone as the reference standard. Thus, the 0.625 mg Premarin tablet was assigned this value because it contained estrogenic potency that, in the rat model, was equivalent to 0.625 mg of sodium estrone sulfate.

In 1970, the United States Pharmacopeia (USP) published monographs for conjugated estrogens and conjugated estrogens tablets, establishing the first compendial standards for these products.² The USP described conjugated estrogens as containing

sodium estrone sulfate and sodium equilin sulfate.³ This description appears to have been based on the known quantity, in Premarin, of each of the two ingredients as well as their demonstrated clinical estrogenic effects.^{3,4,5} The two compounds were known to be the most abundant estrogens in Premarin. Clinical data showing estrone to be an active estrogen were available, and small-scale clinical studies of sodium equilin sulfate indicated that it was a more potent estrogen than estrone.⁶ Limited data from a study completed in 1963 and published in 1971 suggested that sodium 17 α -dihydroequilin sulfate, the third most abundant estrogen, had little clinical activity.⁷

With the publication of the monographs in 1970, the rat potency test was eliminated and replaced by a chemical assay for the two active ingredients. However, the traditional strength assignment was maintained, even though the tablets contained fewer milligrams of sodium estrone sulfate and sodium equilin sulfate than the milligram dose stated on the label.

In 1972, FDA published an assessment of the effectiveness of Premarin.⁸ Drugs such as Premarin that were approved prior to 1962 were required to demonstrate safety but not effectiveness at the time of approval. In 1962, enactment of the Harris-Kefauver amendments to the FD&C Act created a requirement for a demonstration of the effectiveness of new drugs including new drugs approved between 1938 and 1962 (Pub. L. 87-781, 76 Stat. 780). FDA contracted with the National Academy of Sciences/National Research Council to carry out the Drug Efficacy Study to assess the evidence of effectiveness available for new drugs approved prior to 1962. FDA then implemented the results in an effort known as DESI (Drug Efficacy Study Implementation). The 1972 Federal Register notice announced FDA's conclusion that a number of estrogen products, including Premarin, had been shown to be effective for menopausal symptoms (and several other conditions) based on the DESI Panel recommendations and other available evidence. FDA also found that the listed estrogen products were "probably effective" for prevention of

⁸In the preamble to the final rule implementing Title I of the Drug Price Competition and Patent Term Restoration Act of 1984, FDA stated that, although in most cases the Agency will consider an active ingredient to be the same as that of the reference listed drug if it meets the standards of identity described in the USP, "in some cases, FDA may prescribe additional standards that are material to an ingredient's sameness." (See Federal Register, Vol. 57, p. 17950, 17959, April 28, 1992.) See also 21 C.F.R. 5 320.1(c), which states that an identical active drug ingredient may meet "identical compendial or other applicable standards" (emphasis added). FDA applies current scientific knowledge in making its regulatory decisions, even if that knowledge has not yet been incorporated into the USP monograph.

osteoporosis. For indications found to be "probably effective," FDA required sponsors to either submit substantial evidence of effectiveness or remove the indication from the product labeling within a certain period of time.

In 1978, Ayerst Laboratories proposed that conjugated estrogens be required to contain seven estrogenic components. Ayerst subsequently modified this proposal to request only that 17 α -dihydroequilin be added to the existing USP monograph.⁹ In 1982, FDA and USP convened a public meeting to discuss Ayerst Laboratories' proposal that the monograph for conjugated estrogens include 17 α -dihydroequilin.¹⁰ FDA stated at that time that the composition of conjugated estrogens should be determined by estrogenic potency and that the proposed compound had low potency and likely did not contribute to the clinical effect. USP determined that 17 α -dihydroequilin should not be added to the monograph as an active ingredient.

In 1980, FDA published the first version of the document now known as the *Approved Drug Products with Therapeutic Equivalence Determinations*, also known as the "Orange Book."¹¹ This document lists the FDA assignment of therapeutic equivalence among duplicate drug products based on available data pertaining to their pharmaceutical equivalence and bioequivalence. Existing conjugated estrogens tablet products were classified as "BS," i.e., not considered therapeutically equivalent, because of concern that the USP monograph specifications for estrone sulfate and equilin sulfate were inadequate to ensure that products meeting the monograph standard would necessarily produce equivalent therapeutic effects in patients.¹² The "BS" code is used by FDA to indicate that drug products are not considered therapeutic equivalents due to deficient drug standards.

In 1986, FDA announced in the *Federal Register* that a 0.625 mg dose of Premarin daily was found to be effective for prevention of osteoporosis in postmenopausal women.¹³ Two dose response studies evaluating the effect of Premarin on bone mineral density had been published in the literature.^{14,15}

In 1986, while developing an appropriate *in vitro* dissolution test standard for conjugated estrogens bioequivalence testing, FDA discovered that Premarin tablets were a modified release dosage form.¹⁶ This unexpected characteristic of the Premarin formulation meant that generic copies were unlikely to be bioequivalent unless they also had similar modified release characteristics. Because of this discovery, FDA changed the "Orange Book" code for generic conjugated estrogens tablets from "BS" to "BP."¹⁷ The code "BP" means that generic products so

labeled are not considered therapeutically equivalent due to a potential bioequivalence problem. FDA then began to require that generic conjugated estrogens products demonstrate bioequivalence through *in vivo* human subject bioequivalence testing.¹⁸ Because bioequivalence testing is ordinarily performed on the active ingredients of a product, the question of the active ingredients of Premarin again was raised.

In 1989, FDA's Fertility and Maternal Health Drugs Advisory Committee considered the question of the active ingredients in Premarin.¹⁹ The Committee agreed that sodium estrone sulfate and sodium equilin sulfate are active ingredients, but could not reach a consensus on whether or not other estrogens in Premarin were active ingredients.²⁰ In 1990, an Ad Hoc Subcommittee of the Fertility and Maternal Health Drugs Advisory Committee met to consider Premarin bioequivalence issues.²¹ Again, the group agreed that the two named active ingredients were correctly designated, but could not reach a consensus on whether additional components should be regarded as active ingredients.²²

In 1990, FDA published a proposal to withdraw approval of the "BP" coded generic conjugated estrogens formulations for which therapeutic equivalence could not be ensured.²³ The proposal included withdrawing all generic conjugated estrogens marketed at that time. The Agency withdrew approval for these products in 1991, and there are currently no approved generic conjugated estrogens tablets on the U.S. market.^{24,25}

In February 1991, FDA's Generic Drugs Advisory Committee met to consider issues of pharmaceutical equivalence and bioequivalence for conjugated estrogens.²⁶ FDA proposed to the committee that three of the additional estrogens in Premarin be recommended for inclusion as "concomitant components" in the USP monograph for conjugated estrogens.^{27,28} These particular "concomitant components" would be required to be in the product, but would not be considered active ingredients and, thus, would not need to be included in bioequivalence testing.²⁹ The Generic Drugs Advisory Committee endorsed this proposal.³⁰ Subsequently, the USP monographs on conjugated estrogens were amended to include the three additional "concomitant components."³¹

On November 30, 1994, Wyeth-Ayerst submitted a citizen petition requesting, among other things, that FDA not approve any generic conjugated estrogens products that do not contain the compound sodium $\Delta^8,9$ -dehydroestrone sulfate (DHES).³² Wyeth-Ayerst also submitted a petition for a stay of action requesting that FDA stay any decision to "receive" an ANDA for a conjugated estrogens product that does not contain DHES and stay any approval of such an application until FDA responds to the petition.³³

Because of the complex scientific issues associated with determining the active ingredients of conjugated estrogens, in the summer of 1995, CDER formed an Ad Hoc Conjugated Estrogens Working Group to consider these issues. That group of CDER staff examined available data related to the composition of conjugated estrogens and prepared a background document for the Fertility and Maternal Health Drugs Advisory Committee.

On July 27-28, 1995, FDA's Fertility and Maternal Health Drugs Advisory Committee, with representation from FDA's Generic Drugs Advisory Committee and FDA's Endocrinologic and Metabolic Drugs Advisory Committee, heard presentations and discussions on the composition of conjugated estrogens.³⁴ At the end of the deliberations, in answer to questions regarding what additional components, if any, beyond the two recognized active ingredients contribute to the clinical safety and effectiveness of Premarin, the Committee voted unanimously in favor of the following statement:

The Committee feels that insufficient data were presented to determine whether or not any individual component of Premarin or any combination of components in Premarin other than estrone sulfate and equilin sulfate must be present in order for Premarin to achieve its established levels of efficacy and safety [emphasis added].³⁵

On November 1, 1996, FDA completed a "Preliminary Analysis of Scientific Data on the Composition of Conjugated Estrogens."³⁶

On May 1, 1997, the Ad Hoc Conjugated Estrogens Working Group completed its final report providing a scientific background for the Center's decision regarding the composition of conjugated estrogens.³⁷

The regulatory history of conjugated estrogens reflects the complexity of the scientific issues involved. FDA's positions on these issues have evolved over time as new information has become available. As with any such complicated scientific issue, differences in scientific opinion arose and continue to exist concerning how available data are to be interpreted and applied in the regulatory context. These differing views were considered in reaching the CDER position described in this memorandum. Three of these views were recently documented in memoranda to the Director, CDER, and are representative of the spectrum of views expressed during the Center discussions of these issues.^{38, 39, 40}

IV. Characterization of Premarin

A. FDA's Historical Position On The Active Ingredients Of Premarin

Although FDA's Scientific Advisory Committees were unable to provide definitive advice on this issue, FDA continued to support the position taken in the 1970 USP monograph¹ that the ingredients sodium estrone sulfate and sodium equilin sulfate are the sole active ingredients in Premarin. The reasons for this position were as follows:²

1. Until recently, the scientific belief had been that all estrogens were similar in their pharmacologic actions on the body, i.e., "an estrogen is an estrogen." Therefore, the pharmacologic activity of an estrogen preparation could be described in terms of its total estrogenic potency. It was believed that the effects of different estrogens in a mixture were additive and that the identity of the particular estrogen contributing the estrogenic potency was not crucial. Epidemiologic data did not reveal safety or effectiveness differences among various estrogen preparations used for hormone replacement therapy.

As a result, Premarin has historically been defined in terms of total estrogenic potency rather than the sum of the potencies of various components. In 1970, when the first USP monograph was published, 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. Much of Premarin's estrogenic potency for menopausal symptoms can be attributed to the effects of estrone and equilin.

2. Available data on the detailed composition of Premarin and the pharmacologic activity of its components were limited. Much of the available data indicated that many compounds found in Premarin were present in small amounts and had weak estrogenic activity.
3. Based on the results of early studies, including studies of Premarin, the effects of estrogen on bone mineral density appeared to have a very steep dose-response relationship, and the 0.625 mg dose of Premarin appeared to be near the top of the dose response curve. Therefore, small differences in the estrogenic potency of conjugated estrogens

preparations, resulting from omission of components from generic copies, would not be clinically meaningful.

4. In addition, the monograph ranges for the content of sodium estrone sulfate and sodium equilin sulfate in conjugated estrogens are wide.³ Therefore, it was believed that minor differences in estrogen content between synthetic generic products and Premarin due to the absence in the generic copies of several minor Premarin constituents could not make a clinically meaningful difference. (Note: the percent coefficient of variation of sodium estrone sulfate is 1.98, and of sodium equilin sulfate is 3.01, based on percent estrogen composition in 500 batches of Premarin Tablets.⁴)

B. The Center's Current Position On Premarin's Active Ingredients

For the reasons described below, the Center's current position is that Premarin is not sufficiently characterized at this time to determine all of its active ingredients.

1. Emerging scientific evidence demonstrates that all estrogens do not exert their effects in a uniform manner with respect to different target tissues. These differential effects may be due to variable pharmacokinetics,⁵ tissue metabolism, tissue-specific receptor factors, or additional reasons.^{6, 16, 47, 48, 49, 50} For example, clinical studies have shown that the potency of equilin sulfate relative to estrone sulfate varies depending on the pharmacodynamic⁴ effect being studied.^{51, 7} A dose of equilin sulfate that is equipotent to estrone sulfate using one parameter may be more or less potent when evaluated using a different measure. For this reason, the active ingredients of Premarin cannot be defined solely in terms of overall estrogenic potency in any single system, but must be defined based on their contributions to particular estrogenic effects.

⁵Pharmacokinetics can be defined as drug absorption, excretion, metabolism, or distribution.

⁴Pharmacodynamics can be defined as a pharmacologic or clinical response to a given concentration [of a drug] in blood or other tissue (58 FR 39403, July 27, 1993).

Put simply, the new scientific evidence shows that one estrogen can be more active than another in a specific tissue or organ, such as breast, uterus, or bone. The most striking example of this is the synthetic estrogen analog tamoxifen, which blocks estrogen actions in breast tissue, but has estrogen-like activity on bone. These new findings have stimulated extensive research into new pharmaceuticals that could have selective actions on specific tissues and thus might provide beneficial hormone replacement therapy without some of the undesirable side effects, or could be useful in the treatment of cancer or other conditions.

2. Compositional analysis of Premarin using modern analytical techniques demonstrates that it consists of a mixture of a substantial number of compounds with potential pharmacologic activity. In fact, the steroidal content of Premarin has not been completely defined.⁵² Undoubtedly, many of the compounds present in Premarin do not provide a clinically meaningful contribution to the therapeutic effects of the drug and are best thought of as impurities. However, the clinical tests, on which the findings of the safety and efficacy of Premarin were based, were performed on the entire mixture, not on individual components. A basic understanding of the chemical composition of Premarin must be achieved as a first step in adequately characterizing the product, unless a complete understanding of which components provide a meaningful clinical contribution to the effects of the product is achieved by clinical trials alone.

3. Clinical studies have revealed that the assigned potencies of Premarin tablets, which were based on the rat bioassay, do not correctly reflect the tablets' relative potencies in human studies.^{50, 51, 7, 53} For example, clinical studies have shown that Premarin is between 1.4 and 2.5 times more potent than estrone sulfate for suppression of FSH and menopausal symptoms in postmenopausal women.^{50, 7} Because the human studies evaluating the relative potency of Premarin have been small, a precise estimate of the estrogenic potency of Premarin relative to estrone sulfate has not been determined. Because the relative potencies of Premarin, estrone sulfate, and equilin sulfate are not clearly established, it is not possible to tell how much of the effect of Premarin can be accounted for by the effects of equilin sulfate and estrone sulfate. Measuring these effects is further complicated by the

fact that the importance or contribution of each ingredient may depend on the tissue that is being tested, e.g., bone, breast, pituitary, or uterus.

4. New clinical studies have clearly demonstrated that there is a dose-response relationship between estrogen administration and bone mineral density in postmenopausal women.^{34,35} It follows that ensuring an equivalent estrogenic potency is important in the approval of generic copies of estrogen products intended for prevention of osteoporosis. In other words, it is important for the osteoporosis indication that synthetic generic conjugated estrogens based on Premarin have estrogenic strength that is identical to the Premarin tablet.
5. The recent findings with regard to $\Delta 8,9$ -dehydroestrone sulfate (DHES) illustrate a number of the above points. This compound was first detected in Premarin in 1975.^{36,37} DHES represents only a small percentage of the estrogenic compounds present in the product: 4.4% of the "label claim" (i.e., 4.4% of 0.625 mg or approximately 0.0275 mg of DHES per 0.625 mg tablet). (Note: Premarin also contains a small amount of the DHES metabolite sodium 17β - $\Delta 8,9$ -dehydroestradiol sulfate.³⁸ This metabolite comprises approximately 0.003 mg per 0.625 mg tablet. Therefore, the total DHES plus sodium 17β - $\Delta 8,9$ -dehydroestradiol sulfate content of a 0.625 mg tablet is about 0.03 mg or approximately 5% of label claim.) Until recently little has been known about DHES or sodium 17β - $\Delta 8,9$ -dehydroestradiol sulfate.

Pharmacokinetic studies submitted by Wyeth-Ayerst demonstrate that, after single or repeated oral dosing of Premarin in women, the plasma concentration or AUC's of the (conjugated plus unconjugated) 17β - $\Delta 8,9$ -dehydroestradiol metabolite of DHES is the same order of magnitude as the concentration of the 17β -diol metabolites of the active ingredients estrone and equilin.^{39,40,41} The 17β - $\Delta 8,9$ -estradiol concentration is approximately 34% of the combined concentrations of the 17β -diol metabolites of estrone and equilin, or 26% of the 17β -diol metabolites from the three estrogens. The finding that a low-level (5%) component of the tablet would generate a significant concentration of a potentially active metabolite was completely unexpected and illustrates the longstanding inadequate characterization of Premarin. These pharmacokinetic

data do not themselves prove that the DHES in Premarin makes a clinically meaningful contribution to the therapeutic effect of Premarin. However, preliminary clinical studies indicate that the potency of DHES may be similar to that of equilin. (See detailed discussion below.)

6. Based on this new scientific information, the Center concludes that Premarin is not adequately characterized and that, therefore, at this time, its active ingredients cannot be fully determined. Additional information on both composition and relative potencies of components will be necessary to adequately characterize this product. This conclusion is in agreement with the findings of FDA's Fertility and Maternal Health Advisory Committee at its July 27-28, 1995, meeting on this subject."

C. Unresolved Issues Concerning the Current Characterization of Premarin

Products such as Premarin, that are derived from natural source material, frequently are not characterized as completely as synthetic products at the time of marketing. For the purposes of this memorandum, the term "adequate characterization" is intended to mean an amount of scientific information on a product that is sufficient to determine what constituents in the product are responsible for making clinically meaningful contributions to its therapeutic effects. In other words, it is possible to define the active ingredients of a product that is adequately characterized.

There are at least two possible ways to characterize a product. The most straightforward method includes, first, chemical analysis to determine what components are present at significant levels in the product. The interpretation of "significant levels" cannot be exact and would depend on the specific product; however, it is desirable that components present at the 0.1% level or greater be identified and quantified. Once the components of the product are identified, the next step in characterization would be to determine which of them have potential human pharmacologic activity. Such a determination may be based on the following: the quantitative amount in the product, structure-function relationships, *in vitro* tests, animal studies, human studies, or a combination of these. Finally, for components that may contribute to the therapeutic effect based on potential pharmacologic activity, a study could be

conducted comparing the effects of each component alone, and in combination with additional components, to the effects of the entire product, to demonstrate that the "candidate" components achieved all of the therapeutic effects of the product.

Alternatively, in cases where there is some confidence that the "candidate" active ingredients have all been identified, even though the product is not fully chemically characterized, a head-to-head comparative dose-response clinical trial comparing the effects of the combined "candidate" active ingredients against the original product, could, if carried out carefully, demonstrate that the combination contributed all the clinically meaningful therapeutic effects of the original product. This approach might not clearly identify which of the "candidates" were actually active, but could ensure that the combination tested included all of the active ingredients in the product.

The following sections discuss the available scientific evidence on the characterization of Premarin.

1. Composition

At least ten estrogenic compounds have been identified and quantified in Premarin. The composition data for the ten estrogenic compounds cited in the Conjugated Estrogens, USP monograph, and listed in Table 1, were generated by the Center's Division of Drug Analysis from an analysis of two batches of Premarin 0.625 mg tablets.⁶² These results agree generally with other data available to the Center.

Table 1

<u>Sodium Estrogen Sulfate</u>	<u>Mg/Tablet</u>
Estrone	0.370
Equilin	0.168
17 α -Dihydroequilin	0.102
17 α -Estradiol	0.027
17 β -Dihydroequilin	0.011
17 α -Dihydroequilenin	0.011
17 β -Dihydroequilenin	0.021
Equilenin	0.015
17 β -Estradiol	0.005
A8,9-dehydroestrone	0.026

pharmacokinetic data on Premarin components and metabolites, presented in Addendum 2, dated March 31, 1997, to the OCPB Report,⁷³ and also in information submitted to the docket by Wyeth-Ayerst on March 11, 1997,⁶¹ confirm the original finding discussed in the OCPB Report.

Table 2 is derived from pharmacokinetic data submitted by Wyeth-Ayerst based on seven-day dosing of women with two 0.625 mg tablets daily.⁶¹ The steady-state AUC data are calculated from day seven plasma sampling. Table 2 summarizes the relationships among oral dose, total ketone, and total diol for three estrogens.

Table 2 - Results of Pharmacokinetic Studies

Estrogen	Estrone	Equilin	$\Delta 8, 9$ -DHE
Measured dose or AUC			
mg per 2X 0.625mg tab	0.740	0.336	0.052
Total plasma ketone (ng·hr/mL)	94.200	43.145	13.610
Uncon. plasma ketone (ng·hr/mL)	4.083	1.201	0.072
Total plasma 17 β diol (ng·hr/mL)	8.565	10.623	6.624
Uncon. plasma 17 β diol (ng·hr/mL)	0.659	1.060	0.331

The pharmacokinetics of Premarin components are complex, as revealed in these data. Estrone, equilin, $\Delta 8, 9$ -dehydroestrone, their active 17 β -reduced metabolites, and other estrogenic components of Premarin circulate in the plasma both as the conjugated (primarily sulfate ester) and unconjugated derivatives and with various degrees of protein binding, as discussed in the OCPB Report. There is interconversion between the ketone and 17 β -reduced forms of each estrogen and among the conjugated and unconjugated derivatives. The degree of protein binding of each derivative may be important to its clinical activity.

Put simply, this information shows that there is not a one-to-one relationship between the amount of each estrogen in the tablet and the amount of active forms

(derivatives) of that estrogen in the blood. Each of the three estrogens evaluated in this clinical trial distributes differently into its derivatives in the body. This means that each of the three estrogens might cause different effects simply as a result of these distributional differences.

The actual magnitude of the contribution of each derivative of any component estrogen to the overall estrogenicity of Premarin is not well understood. As just stated, the pharmacokinetic data show that the ratios of the concentrations of the different derivatives are distributed differently for those estrogens that have been studied: estrone, equilin, and DHE. If there are tissue-specific effects of derivatives, then the size of a derivative's contribution could vary depending on the tissue tested. The available data suggest that these tissue-specific differences exist. For example, *in vitro* potency data for estrone and 17β -estradiol were submitted by Wyeth-Ayerst.⁷⁴ When potency was tested by estrogen receptor binding, estrone was shown to be much less potent than estradiol (about 200 times less), as has been previously shown by receptor binding and cellular assays. In contrast, when potency testing was performed in a liver (Hep-G2) cell line using functional activation, estrone's potency appeared to be of the same order of magnitude as estradiol's potency. The experimenters were able to show that this increased potency of estrone resulted from its conversion to estradiol by the cells. Therefore, in tissues that have the capability to metabolize ketone forms to diols (e.g., estrone to estradiol), circulating ketone forms could make a large contribution to observed effects in that tissue. Similarly, conversion of conjugated (sulfated) forms of circulating estrogens to the unconjugated forms has been shown to occur in target tissues such as breast.⁷⁵ In these tissues, total estrogen concentrations (i.e., conjugated plus unconjugated) may be more important than in tissues that cannot convert the conjugated forms to the active, unconjugated forms.

One striking finding in the pharmacokinetic data is the differences in the proportions of the 17β -diol concentrations resulting from the three estrogens (sodium estrone sulfate, sodium equilin sulfate, and DHES), compared to the ratios of the three estrogens in the tablet. It is known that the 17β -diol derivatives

of equilin and estrone are potent estrogens. The pharmacokinetic data as a whole show that, after dosing with Premarin, the plasma concentration of unconjugated 17β -dihydroequilin is about twice (1.6 times) as high as the concentration of 17β -estradiol, even though there is only about half as much equilin as estrone in the tablet. The difference in the concentration of the active metabolite may account for the known greater clinical estrogenic potency of equilin. As discussed above, an unexpected finding from the pharmacokinetic data in the Missouri study, the most reliable data generated to date, was that the plasma concentration of unconjugated 17β - $\Delta 8,9$ -dehydroestradiol is about half the concentration of unconjugated 17β -estradiol, even though there is more than ten times more estrone sulfate than DHES in Premarin. This may account for the high oral potency of DHES that has been found in the limited clinical studies performed with this compound.^{76,77}

Put simply, these data show that a dose of DHES results in a much higher blood level of the active metabolite than would result from the same dose of estrone sulfate. This finding alone suggests, but does not prove, that a low dose of DHES could have a much larger than expected effect.

The above pharmacokinetic data provide a basis for beginning to understand the complex relationship between the composition of Premarin and its clinical effects. However, this understanding is still incomplete. The pharmacokinetics must be understood in the context of pharmacodynamic properties of the various components, including their clinical effects.

3. Clinical effects of Premarin

Premarin and certain Premarin components have been tested fairly extensively in animals, particularly rodents. Animal data, either *in vitro* or *in vivo*, have not proven to be quantitatively predictive of the effects found in women.⁷⁸ Therefore, animal tests, while useful in screening compounds for activity, cannot be used to definitively assign human clinical effects. The most confident conclusions can be drawn from human clinical testing. The following summarizes what is known about the contribution of Premarin components to its overall activity from *in vitro* or *in*

vivo human testing.

a. Pharmacodynamics of Premarin and Some of Its Components

The term "pharmacodynamics" refers to pharmacologic or clinical responses to a given concentration of a drug in blood or other tissue.* For example, raising or lowering blood pressure, causing dry mouth, or constricting the pupils are pharmacodynamic effects of various drugs. Pharmacodynamic effects can be beneficial, harmful, or neutral. The benefits of most drugs derive from their desired pharmacodynamic effects, while drug side effects often result from undesirable pharmacodynamic activity.

Premarin and its components, like other estrogens, affect a wide variety of human tissues, including pituitary, breast, uterus, bone, liver, and endothelium.⁷ Some of these actions result in the beneficial effects of the drug, some cause side effects, and some (for example, cardiovascular or lipoprotein effects) have not been definitively evaluated. There are studies in the literature of effects of estrogen on each of these tissues, especially effects on the pituitary, uterus, and bone. This section discusses the pharmacodynamic effects of Premarin and its components other than the relief of menopausal symptoms and prevention of osteoporosis.

A dose-response relationship exists between estrogen treatment and FSH suppression.⁷⁹ Some pharmacodynamic data on suppression of FSH, including dose-response data, exist for equilin sulfate, estrone sulfate, and Premarin (see also menopausal symptoms, below).^{6,7,50,80} In a study of suppression of urinary gonadotrophins, equilin was found to be about twice as potent as Premarin and five times more potent than estrone sulfate for this effect, while Premarin was 2.5 times more potent than estrone sulfate.⁷ In studies of human serum FSH levels, Premarin has been found to be about 1.4-2.0 times as potent as estrone sulfate.^{81,50} These studies are in relative agreement.

The published data on the effects of Premarin and its components on uterine or vaginal markers are limited.

*See footnote c, supra.

Beck and Friedrich found equilin sulfate to be 2-3 times more potent than Premarin for effects on vaginal epithelium and endometrium.⁸² Varma et al found Premarin to be twice as potent as estrone sulfate for endometrial changes.⁸¹ Geola et al evaluated the dose-response relationship between Premarin and vaginal cytologies and concluded that 1.25 mg Premarin daily was necessary for achieving full replacement levels for this parameter.⁸⁰ These studies are not adequate for drawing firm conclusions about the relative contributions of equilin and estrone to the effects of Premarin on uterine or vaginal markers.

A number of studies of Premarin or its components have evaluated pharmacodynamic markers of bone effects.^{51, 75, 79, 80, 83} Jones et al estimated that Premarin was twice as potent as estrone sulfate for reduction of the urinary calcium/creatinine ratio. This ratio is a measure of bone resorption. Geola et al performed a dose-response study evaluating the effect of Premarin on the calcium/creatinine ratio, and found that 0.3 mg Premarin was the lowest dose to have a significant effect. Lobo et al found that Premarin was twice as potent as both estrone sulfate and equilin sulfate for reduction of the urinary calcium/creatinine ratio. The Lobo finding of a significant effect of 0.3 mg Premarin was not duplicated in a larger study by Lindsay et al.¹⁵ Because of limitations in study designs and because the pharmacodynamic markers for bone are not sufficiently quantitative, no conclusions about comparative pharmacodynamic effects on bone of Premarin or its components can be drawn from these results.

Data on Premarin or Premarin component effects on lipoproteins and other plasma proteins, or other pharmacodynamic markers are quite limited.^{50, 51, 53, 49, 84} Having information about these effects is important for several reasons. Stimulatory effects on liver proteins may affect drug safety. In addition, as discussed in the OCPB Report,⁷¹ levels of circulating unconjugated estrogens may be affected by binding to plasma proteins, particularly sex hormone binding globulin (SHBG). Stimulation of SHBG could alter drug availability. Available data suggest that certain Premarin components differ in the ability to stimulate SHBG.⁵⁰ Human pharmacodynamic data on DHES submitted by Wyeth-Ayerst demonstrated that 1.25 mg estrone sulfate had a much greater effect on SHBG levels than did 0.125 mg DHES;⁸⁵ however, this result requires

confirmation.

Taken as a whole, the available pharmacologic data demonstrate that estrone sulfate (as the piperazine salt), equilin sulfate, and Premarin have different pharmacodynamic effects when potency on various tissues is evaluated.^{50, 51, 7, 53} For example, in a single study, Premarin was found to be 1.4 times more potent than piperazine estrone sulfate (expressed as the sodium rather than piperazine salt) for FSH suppression, a pituitary effect.⁵⁰ In contrast, Premarin was 3.5 times more potent than estrone sulfate for stimulation of angiotensinogen and 3.2 times more potent for stimulation of sex hormone binding globulin (SHBG). Presumably, this difference arises because other components of Premarin contribute to these effects in a manner different from estrone sulfate. It is not known if these differential pharmacodynamic effects are completely attributable to the presence of equilin sulfate.

In summary, the two Premarin components that have been carefully studied, equilin sulfate and estrone sulfate, differ from each other and from Premarin in pharmacodynamic profile. It is not well understood which of the pharmacodynamic actions are desirable and which contribute to unwanted side effects. Adequate characterization of Premarin will require an understanding, based on scientific data, of those Premarin components that contribute to the pharmacodynamic effects of Premarin.

b. Clinical Effects of Premarin Components

i. Menopausal symptoms

A number of clinical studies evaluating Premarin and Premarin components for the treatment of menopausal symptoms have been performed.^{79, 80, 82, 86} Equilin sulfate has been found to be about three times more potent than Premarin for alleviating vasomotor symptoms.⁸² The data submitted by Wyeth-Ayerst on DHES show that DHES is more potent than estrone sulfate for these effects, but the data are not adequate to precisely assign a potency.⁷⁶ Without dose-response studies to determine the potency of DHES for menopausal symptoms relative to the potency of estrone sulfate and equilin sulfate, the contribution of

DHES to the activity of Premarin in treating menopausal symptoms cannot be determined. Similarly, without a head-to-head comparison of the dose-related effects of Premarin, estrone sulfate, and equilin sulfate in the treatment of menopausal symptoms, the extent of contribution of the two components to the overall estrogenic potency of Premarin for this effect also cannot be accurately determined, although it is clear that both contribute.

ii. Osteoporosis prevention

Use of surrogate markers. The goal of preventive therapies for osteoporosis is the prevention of fractures and deformity. For estrogens, FDA accepts measurement of bone mineral density as an adequate surrogate for preventing these longer term clinical outcomes.⁸⁷ A number of other markers for evaluating pharmacodynamic effects on bone have been developed.⁸⁸ None of these other markers is sufficiently well understood or quantitative to permit its use as a surrogate for osteoporosis prevention effects. Therefore, in the absence of other validated surrogate markers, definitive data on bone effects must come from human trials evaluating bone mineral density, fractures, and/or deformity.

Use of blood 17 β -estradiol levels as a surrogate marker. Comments submitted to the docket of Wyeth-Ayerst's citizen petition,⁸⁹ as well as statements in the scientific literature, assert that achievement of certain levels [e.g., 39 pg/ml (Palacios et al) or greater than 60 pg/ml (Reginster et al)] of serum 17 β -estradiol is an adequate surrogate for preservation of bone mineral density because there is a strong correlation between the two both in clinical trials and in untreated perimenopausal women.^{83, 90}

The study by Palacios et al evaluated women who had undergone surgical menopause and who were randomized to percutaneous estradiol, conjugated estrogens (source unspecified), or no therapy over two years. Untreated women lost a mean of 9% of spine bone mineral density over two years, whereas the estradiol treated group and the conjugated estrogens treated group gained 4.1% and 5.6%

spinal bone mineral density respectively. Women treated with percutaneous estradiol were reported to have a mean serum estradiol level of about 80 pg/ml over the course of the study. The conjugated estrogens treated women had a mean serum estradiol level of about 40 pg/ml. It is not possible to conclude anything about a protective level of 17β -estradiol from the conjugated estrogens arm of this study since conjugated estrogens also contain, at a minimum, equilin and possibly other components that contribute to the effect on bone. The value of 80 pg/ml from the percutaneous estradiol arm is not inconsistent with the data reported by Reginster et al who found that circulating level of 17β -estradiol between 60-90 pg/ml correlated well with pharmacodynamic markers of beneficial bone effects. This correlation suggests, but does not prove, that estrogen replacement therapies achieving such levels of circulating estradiol may be effective in preventing bone loss.

FDA does not currently accept 17β -estradiol levels as an adequate surrogate for osteoporosis prevention in women. Trials of bone mineral density are required. In addition, the available data do not indicate that the potentially protective levels of 17β -estradiol are attained after administration of Premarin.

The Palacios study found that treatment with conjugated estrogens 0.625 mg resulted in a mean estradiol level of 40 pg/ml, which is below the 60 pg/ml minimum suggested by Reginster. However, the Librach and Nickel study submitted to the docket, as well as the Reginster study and other data reported in the literature, found that serum levels of 17β -estradiol above 60 pg/ml are achieved in women treated with Premarin or a Canadian generic copy of Premarin^{89,91}. In the Librach and Nickel study, women treated with Premarin achieved a 17β -estradiol level of 85.5 pg/ml while women treated with the Canadian product had mean serum levels of 94.9 pg/ml. These differences appear to relate to problems with analytical methodology, possible due to cross-reactivity of radio-immunoassay reagents with other components in Premarin. When serum 17β -estradiol is measured by direct chemical

means, the high 17β -estradiol levels are not found in women treated daily with 0.625 mg Premarin.^{60,61} This latter finding is corroborated by data from a study of the effects of esterified estrogens (Estratab, USP) on bone mineral density, which was recently presented in abstract.⁶² In this study, daily dosing with 0.625 mg of esterified estrogens, which contains approximately 0.518 mg sodium estrone sulfate⁶³ (0.625 mg Premarin contains about 0.370 mg sodium estrone sulfate) resulted in a mean plasma concentration of 17β -estradiol of 40 pg/ml. In addition, in this same study, daily administration of 0.3 mg esterified estrogens, which contain about 0.248 mg sodium estrone sulfate, resulted in a mean plasma concentration of 26 pg/ml of 17β -estradiol. These results are inconsistent with the serum level results presented by Librach and Nickel, but generally agree with Palacios' findings and with Wyeth-Ayerst's bioavailability data. Therefore, the available data on serum 17β -estradiol levels do not indicate that levels over 60 pg/ml are attained with the dose of Premarin recommended for the prevention of osteoporosis.

Clinical effects on bone. The clinical effects of Premarin on bone are well established. A number of clinical trials have confirmed the effects of Premarin in preserving and increasing bone mineral density in postmenopausal women.^{14,15,94} Ettinger et al demonstrated in a nonrandomized trial that 0.3 mg Premarin, when administered with calcium supplementation, was adequate to prevent bone mineral loss in the spine and hip.⁹⁵ The recent PEPI trial demonstrated that the currently recommended 0.625 mg dose of Premarin resulted in an increase in bone mineral density in women treated for over two years, while untreated women lost bone.⁹⁶

Estrone is approved as a single estrogen (marketed under the brand name Ogen by Upjohn, generic name estropipate), but as a different salt from the estrone in Premarin (the piperazine rather than the sodium salt of estrone sulfate) for the treatment of menopausal symptoms and the prevention of osteoporosis. The recommended dose for osteoporosis is 0.75 mg of estropipate, which is equivalent to 0.625 mg sodium estrone sulfate.

A dose-response study has shown that a dose equivalent to 0.300 mg estrone sulfate, combined with 1 gram daily calcium supplementation, is not effective in preserving bone mineral density.⁵⁷ In this study, 0.625 mg of estrone sulfate resulted in preservation of bone mineral density compared to baseline. There was no statistically significant difference in bone mineral density between patients dosed with 0.625 mg and those given 1.25 mg; however, only the 1.25 mg group had bone mineral densities statistically greater than the placebo group at two-year follow-up. Based on the data from this trial, the amount of estrone sulfate in Premarin (approximately 0.370 mg) is too small to account for all of Premarin's known effects on bone mineral density, so other estrogens present in the product must be contributing to this effect.

Additional information on the effects of equilin on bone has recently become available. On October 30, 1996, Duramed Pharmaceuticals submitted to the docket an abstract of a clinical study that had recently been presented at a scientific meeting.⁵⁸ The study provided new information germane to the clinical effects of Premarin on bone.⁵⁵ This study, sponsored by Solvay Pharmaceuticals, was a clinical trial of their product, Estratab (this trial was also discussed in the section on estradiol blood levels). Estratab is a generic esterified estrogens product. Esterified estrogens USP contain sodium estrone sulfate and sodium equilin sulfate in different amounts than are in Premarin⁵⁹ (based on presentations by Solvay, 0.300 mg of their esterified estrogens product contains approximately 0.248 mg estrone sulfate and 0.038 mg equilin sulfate).⁶⁰ The study was a two-year placebo controlled trial testing three doses of Estratab combined with calcium supplementation in postmenopausal women evaluating bone mineral density and side effects. According to the abstract, all three doses were effective at 12, 18, and 24 months in preserving bone mineral density compared to placebo. The abstract reveals a dose response among the three Estratab doses tested. Also significant is the fact that the lowest dose tested, 0.3 mg Estratab, appeared to be effective in preserving bone mineral density when given continuously in

conjunction with calcium supplementation. There are lower amounts of both estrone sulfate and equilin sulfate in this dose of Estratab than are required to be in the 0.625 mg tablet of generic conjugated estrogens according to the current conjugated estrogens USP monograph. Therefore, if the data in the abstract are correct, it could be concluded that a product containing the amounts of estrone sulfate and equilin sulfate required in the current monograph for conjugated estrogens USP would be effective in preserving bone mineral density when given continuously with supplemental calcium. Since the study by Harris, et al.⁷ showed that 0.3 mg of estrone sulfate alone is not effective in preserving bone mineral density, then it is likely that there was a contribution from the equilin sulfate in the Solvay product, although firm conclusions cannot be drawn from cross-study comparisons. This information addresses to some extent one of the questions raised in FDA's *Preliminary Analysis of Scientific Data on the Composition of Conjugated Estrogens*,³⁶ that is, the fact that the contribution of equilin to preserving bone mineral density had not been demonstrated.

Despite this additional information, the question of what are the active ingredients in Premarin for the indication of maintaining bone is not completely resolved. The Solvay study demonstrated a dose response for bone mineral density. The lowest dose, 0.3 mg, was effective in preserving bone density. The two higher doses, 0.625 mg and 1.25 mg, of esterified estrogen actually increased bone density over the two-year period. This finding is consistent with other published data.^{34,61} In the case of the Solvay study, it is not known whether, at the higher doses, more women responded with bone preservation than at lower doses, or whether women who would have responded to 0.3 mg simply had a larger response to the higher doses. In either case, estrogenic potency has been shown to be important to the clinical effect on bone within this dose range. It has been estimated that a proportion of women taking the recommended dose of Premarin continue to lose bone mineral, even though mean values are sustained or improved.³⁹

The finding that sodium equilin sulfate and sodium estrone sulfate, at the doses present in Estratab, preserve bone mineral density provides support for the proposition that equilin contributes to the bone preservation effects of Premarin. However, as discussed at the beginning of this memorandum, the requirement for approval of an ANDA is not that generic drugs have effects similar to the reference listed drug but, rather, that they have the same active ingredients. Only if the active ingredients are the same can generic copies be relied upon to have the same estrogenic potency and, therefore, the same effects on bone.

Limited data on the pharmacodynamic effects of DHES on bone have been submitted by Wyeth-Ayerst.^{76,77} These data show that DHES has a pharmacodynamic effect on bone markers, but the data do not shed light on whether the DHES component of Premarin has a meaningful clinical effect on bone.

iii. Safety

There are safety concerns about all estrogen preparations currently approved for long-term administration for the prevention of osteoporosis. Long-term estrogen administration is associated with an increased incidence of endometrial cancer in women who have not undergone hysterectomy, and there is an ongoing controversy about the relationship of long-term estrogen replacement therapy to breast cancer.

No head-to-head studies have compared the long-term safety of various estrogen preparations when used chronically for the prevention of osteoporosis. The available epidemiologic evidence, summarized at the July 27-28, 1995, Advisory Committee meeting, does not definitively establish safety differences among various estrogens.¹⁰⁰ Thus, it is not known to what extent, if any, differences in the types of estrogens used may affect safety.

There are no comparative safety trials of Premarin components available. There are few pharmacodynamic markers available with which to

assess safety for effects such as cancer. Therefore, sufficient clinical data do not exist to fully characterize the contributions (either positive or negative) of various Premarin components to its clinical safety.

iv. Other pharmacologic effects.

There is currently intense interest in the role of estrogen replacement therapy (ERT) in the prevention of cardiovascular disease and possibly other age-related disorders in women.¹⁰¹ No estrogen product is currently approved by FDA for such indications. If Premarin were to be found effective for prevention of cardiovascular disease, elucidating the effects of Premarin and its components on relevant pharmacodynamic parameters would be important in fully characterizing the product. There are clinical data suggesting that equine estrogens may have differential effects on parameters such as lipoprotein levels and lipid peroxidation;^{21, 22} however, these data are as yet very incomplete.

4. Inclusion of $\Delta 8, 9$ -dehydroestrone sulfate (DHES).

Many of the issues raised by Wyeth-Ayerst in its citizen petition submitted in November 1994, and addressed in numerous submissions to the docket of the citizen petition, pertain to the need to include DHES in generic copies of Premarin. Although this memorandum is not intended to be a response to the citizen petition and should not be construed as one, the scientific issues related to this compound are addressed below insofar as they relate to the approvability of generic copies of Premarin, which is the subject of this memorandum.

As discussed previously at the beginning of this section (IV.B.5.), DHES is a conjugated estrogens compound that comprises about 4.4% of the "label claim" of Premarin. It has been recognized as a constituent of Premarin for two decades.²⁷ However, little scientific data have been available on its activity, and it has been treated as an impurity. Information submitted by Wyeth-Ayerst on the pharmacokinetics of DHES in Premarin reveal that its metabolite, 17β - $\Delta 8, 9$ -dehydroestradiol, is present in surprisingly large concentrations in the plasma, considering the

composition of the tablet.^{59,60} FDA analyses support this finding.⁷¹ The 17 β -A8,9-dehydroestradiol concentration is important because the diol form of estrogen is usually the most active in the human body. After taking Premarin, the concentration (or AUC) of unconjugated 17 β -A8,9-dehydroestradiol in the plasma is between 50% and 125% (depending on what study results are used) of the concentration of unconjugated 17 β -estradiol and is one third the concentration of unconjugated 17 β -dihydroequilin.

The fact that a compound is present at high concentrations in the plasma does not necessarily mean that it is clinically important. The significance of the finding that 17 β -A8,9-dehydroestradiol is present in high concentrations depends on the potency of 17 β -A8,9-dehydroestradiol compared to the potency of the other circulating estrogens. If it is assumed that the potency of the 17 β -diol metabolites derived from estrone sulfate, equilin sulfate, and DHES have equal potency, then the contribution of DHES to the overall estrogenic activity of the 17 β -diol metabolites of the three estrogens would be 16% (based on unconjugated diol AUCs) to 26% (based on total diol AUCs).⁶¹ However, there are several ways to evaluate relative potency of estrogens. One method, testing in animal species, is useful for determining estrogenicity, but has not proven to be quantitatively predictive for humans (the original rat potency test for conjugated estrogens is a good example). This could be due to interspecies differences in metabolism, some of which have been confirmed.¹⁰²

If animal testing is not adequately quantitative, *in vitro* studies using human cells or receptors may be performed, or human clinical tests may be carried out. Scientific data of both types assessing the relative potency of DHES have been submitted to the docket. Wyeth-Ayerst provided data on human estrogen receptor binding as well as functional activation data in HEP-2 cells.¹⁰³ In addition, Duramed Pharmaceuticals provided data on functional activation of Ishikawa cells, a human uterine cell line.¹⁰⁴ The results of these studies are summarized in the OCPB Report of October 25, 1996,⁷¹ Addendum 1 to that report dated February 12, 1997,⁷² and Addendum 2 to that report dated March 31, 1997.⁷³ These OCPB Reports attempt to quantify the clinical estrogenic contribution to Premarin from

equilin, estrone, DHES, and 17 α -dihydroequilin based on the potencies derived from the various *in vitro* assays in combination with the pharmacokinetic data.

The OCPB Report estimates that, based on the *in vitro* potencies and the known pharmacokinetics, DHES and its metabolite contribute approximately 2.8-6.5% of the overall estrogenic potency of Premarin, depending on the assumptions used.¹⁰⁵

Just as with the animal data, it is important to try to assess how reliably the *in vitro* data predict the actual clinical outcomes. A limitation of cellular assays is that only one tissue type is evaluated. The results of the OCPB analysis shows that widely differing estimates are arrived at depending on the system used.¹⁰⁶ This may be due to artifacts of the system (i.e., metabolism of estrone to estradiol, etc, in the Hep-G2 cells), true tissue differences, or other reasons. The best way to evaluate the *in vitro* potency assignments is to compare their results with known clinical outcomes. In this case, certain comparisons are possible because both estrone sulfate and equilin sulfate have been tested in women as single ingredients.^{51,7} A number of clinical studies have shown that, for both FSH suppression and treatment of menopausal symptoms, equilin sulfate is roughly five times more potent than estrone sulfate when administered as a single ingredient. Comparison of this known clinical fact to the potency estimates in Tables 3 and 4 of OCPB Addendum 2 reveals that the Ishikawa cell potencies do not correctly predict the oral potency of equilin relative to estrone.⁷³ The Ishikawa cell data predict that oral equilin sulfate would be equipotent to or less potent than estrone sulfate. Of the other *in vitro* estimates, the estrogen receptor binding assay best predicts the known differences between equilin and estrone, predicting equilin sulfate to be between two to four times more potent than estrone sulfate depending on the assumptions used. Because of these widely differing estimates, it must be concluded that *in vitro* assays, even in human systems, cannot currently be relied upon to provide precise predictions of relative clinical potencies.

The other information available on the relative potency of DHES comes from human studies. Wyeth-Ayerst submitted the results of two human studies to the

docket.^{76,77} These studies were small, unblinded, uncontrolled trials, and would not be of the type relied upon for determining safety or efficacy of a drug. In addition, they did not use a dosage form equivalent to that of Premarin, and thus their results cannot be directly extrapolated to Premarin. However, they are quite similar to the types of studies that were originally used to evaluate the role of estrone sulfate and equilin sulfate in Premarin and can be used to assess certain comparative pharmacodynamic parameters. In these trials, 0.125 mg of DHES was administered daily to postmenopausal women. This dose of DHES is about four times the amount in a 0.625 mg tablet of Premarin. In both studies, this dose of DHES caused approximately 15-26% suppression of FSH after two weeks of dosing. This is in the range of suppression resulting from 0.625 mg of estrone sulfate reported in the literature.⁵⁰ The study performed in Brazil included a comparison group given 1.25 mg estrone sulfate. This group achieved approximately a 40% reduction in FSH levels at two weeks. This effect is somewhat greater than has been previously reported.^{50,51}

Based on these human data, the oral potency of DHES (for pituitary pharmacodynamic parameters) is (very roughly) five to six times that of estrone sulfate, or very similar to that of equilin sulfate and is about what would be predicted on pharmacokinetic grounds if the estrone and DHE derived diols were roughly equipotent. DHE, like equilin, is a B ring unsaturated estrogen. If DHES has the same oral potency as equilin and if the contributions of estrone sulfate, equilin sulfate, and DHES plus the small amount of 17 β -A α ,9-dehydroestradiol sulfate were to be considered, then DHES and its metabolite would contribute about 9% of the estrogenic potency from these three components, at least for pituitary parameters.

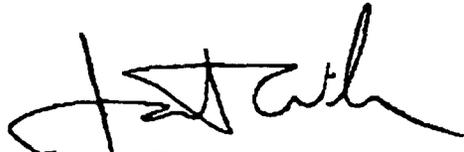
It can be seen from the above analysis that the high end of the estimate of the contribution of DHES to the estrogenic potency of Premarin from the *in vitro* assays is similar to the estimate derived from clinical studies, i.e., about 9%, and both of the estimates are lower than the 16% to 26% estimate based on an assumption that each 17 β -diol metabolite is equally potent. Unfortunately, all of the estimates have problems and uncertainties. A precise estimate of the potency of DHES relative to estrone sulfate is not

available. In addition, none of the data provide insight into the contribution of these components to estrogenic potency with respect to bone. As discussed above, preliminary pharmacodynamic data indicate that DHES has an effect on bone markers. The available data demonstrate that DHES is a potent estrogen and may make a clinically meaningful contribution to the therapeutic effects of Premarin.

V. Conclusions

1. Under the Federal Food, Drug, and Cosmetic Act, for a generic drug product with Premarin as the reference listed drug to be approved, the generic drug must have the same active ingredients as Premarin. This requirement, paired with a showing of bioequivalence of the generic drug to the reference listed drug, is meant to ensure that the data developed by the innovator company to demonstrate the safety and effectiveness of the reference listed drug will support approval of the generic drug. Independent demonstration of safety and effectiveness is not required for approval of generic drugs. Approval of generic copies of Premarin manufactured from combined synthesized components will require data sufficient to demonstrate that such copies contain the same active ingredients as Premarin.
2. The reference listed drug Premarin is not adequately characterized at this time. In particular, the estrogenic potency of the product is not clearly defined relative to the estrogenic potency of its constituents. In addition, the contribution of the two most abundant estrogens, sodium equilin sulfate and sodium estrone sulfate, to the overall estrogenic potency is not well understood. Furthermore, the quantitative composition of Premarin with respect to potentially pharmacologically active components has not been defined. Without this information it is not possible to define the active ingredients of Premarin.
3. Investigations designed to produce the scientific data needed to determine the active ingredients are feasible. Such information would allow a determination of which components of Premarin make a clinically meaningful contribution to its overall effects. It is both feasible and desirable for the constituent active ingredients in Premarin to be characterized to this extent.

4. With regard to sodium $\Delta^8,9$ -dehydroestrone sulfate (DHES), the available scientific evidence indicates that DHES is an active estrogen that contributes to the estrogenic potency of Premarin. The clinical significance of this contribution has not been determined. DHES must be included in generic copies of Premarin unless scientific data are presented that demonstrate that the estrogenic activity of DHES is not clinically meaningful.
5. Despite the fact that at this time Premarin is not adequately characterized, the Agency could approve generic copies of Premarin that originate from the same natural source material (pregnant mares' urine) before the active ingredients are defined, provided that detailed chemical composition of the product is known. This is because Premarin is manufactured and controlled using certain methods, and there could be confidence that generic copies using the same source materials and controlled in the same manner, based on the known composition of Premarin, would have the same level of assurance that the same active ingredients are in the generic product as are in Premarin.
6. In summary, the Center concludes that because the reference listed drug Premarin is not adequately characterized at this time, the active ingredients of Premarin cannot now be defined. Until the active ingredients are defined, a synthetic generic version of Premarin cannot be approved.



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ENDNOTES

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*The Art of Leadership...
The Science of Change*

Duramed Pharmaceuticals, Inc.
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Cincinnati, Ohio 45213
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11

April 9, 1998

Betty Williams, PH, RN, FAAN
President
National Black Nurses Association, Inc.
1511 K Street, NW, Suite 415
Washington, DC 20005

Dear Ms. Williams:

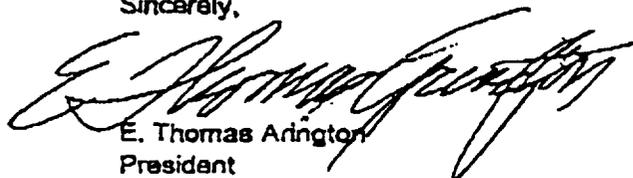
Duramed Pharmaceuticals, Inc. is pleased to inform you that we have filed a New Drug Application with the FDA for synthetic conjugated estrogens tablets (Cenestin™) for the treatment of vasomotor symptoms in postmenopausal women. The basis of this NDA filing is a multi-center, double-blind, clinical trial comparing the effects of 12 weeks of randomized treatment of either Cenestin™ or a placebo tablet on the reduction of hot flashes in 120 postmenopausal women.

In contrast to published clinical studies of other estrogen replacement drug products, the novel design of the Cenestin™ clinical study advanced therapeutic science in that the study participants better reflected the intended patient population. Specifically, the Cenestin™ clinical study included women who were just entering menopause, with no weight restriction or race preference. These inclusion criteria were different in that most published clinical reports include only Caucasian women in later stages of menopause with narrow weight requirements.

The active drug ingredients in Cenestin™ are synthesized from plants and not made from pregnant horse urine. When approved by the FDA, this synthetic conjugated estrogens drug product will provide an economic alternate estrogen replacement therapy to those postmenopausal women who prefer a synthetic choice.

Please feel free to contact John R. Rapoza, M.S., R.Ph., Vice President, Regulatory Affairs, at (513) 458-7274 or the undersigned at (513) 731-9900 should you have any questions about this clinical study or the NDA filing.

Sincerely,



E. Thomas Arlington
President

ETA/nam

Guideline for Industry

The Extent of Population Exposure to Assess Clinical Safety:

**For Drugs Intended for Long-
term Treatment of Non-Life-
Threatening Conditions**

ICH-E1A

March 1995

GUIDELINE FOR INDUSTRY¹

THE EXTENT OF POPULATION EXPOSURE TO ASSESS CLINICAL SAFETY: FOR DRUGS INTENDED FOR LONG- TERM TREATMENT OF NON-LIFE-THREATENING CONDITIONS

The objective of this guideline is to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases. The safety evaluation during clinical drug development is expected to characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. Thus, duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the data base necessary to achieve such goals.

For the purpose of this guideline, it is useful to distinguish between clinical data on adverse drug events (ADEs) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently are nonconcurrently controlled

¹This guideline was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, October 27, 1994. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guidance was published in the Federal Register on March 1, 1995 (60 FR 11270) and is applicable to drug and biological products. In the past guidelines have generally been issued under § 10.90(b) [21 CFR 10.90(b)], which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of revising §10.90(b). Therefore, this guideline is not being issued under the authority of §10.90(b), and it does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind FDA in any way. For additional copies of this guideline, contact the Consumer Affairs Branch (formerly the Executive Secretariat Staff), HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855, 301-594-1012. An electronic version of this guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

studies. It is expected that short-term event rates (cumulative 3-month incidence of about 1%) will be well characterized. Events where the rate of occurrence changes over a longer period of time may need to be characterized depending on their severity and importance to the risk-benefit assessment of the drug. The safety evaluation during clinical drug development is not expected to characterize rare adverse events, for example, those occurring in less than 1 in 1000 patients.

The design of the clinical studies can significantly influence the ability to make causality judgments about the relationships between the drug and adverse events. A placebo-controlled trial allows the adverse event rate in the drug-treated group to be compared directly with the background event rate in the patient population being studied. Although a study with a positive or active control will allow a comparison of adverse event rates to be made between the test drug and the control drug, no direct assessment of the background event rate in the population studied can be made. A study that has no concurrent control group makes it more difficult to assess the causality relationship between adverse events observed and the test drug.

There was general agreement on the following:

1. A harmonized regulatory standard is of value for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions. Although this standard covers many indications and drug classes, there are exceptions.
2. Regulatory standards for the safety evaluation of drugs should be based on previous experience with the occurrence and detection of adverse drug events (ADEs), statistical considerations of the probability of detecting specified frequencies of ADEs, and practical considerations.
3. Information about the occurrence of ADEs in relation to duration of treatment for different drug classes is incomplete, and further investigations to obtain this information would be useful.
4. Available information suggests that most ADEs first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADEs over time.

To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300 to 600 patients should be adequate.
5. There is concern that, although they are likely to be uncommon, some ADEs may

increase in frequency or severity with time or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgement based on the probability of detecting a given ADE frequency level and practical considerations.

100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a one-year exposure period this number of patients can provide reasonable assurance that the true cumulative one year incidence is no greater than 3%.

6. It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500. Japan currently accepts 500 to 1500 patients; the potential for a smaller number of patients is due to the postmarketing surveillance requirement, the actual number for a specific drug being determined by the information available on the drug and drug class.

7. There are a number of circumstances where the harmonized general standards for the clinical safety evaluation may not be applicable. Reasons for, and examples of, these exceptions are listed below. It is expected that additional examples may arise. It should also be recognized that the clinical data base required for efficacy testing may be occasionally larger or may require longer patient observation than that required by this guideline.

Exceptions:

a. Instances where there is concern that the drug will cause late developing ADEs, or cause ADEs that increase in severity or frequency over time, would require a larger and/or longer-term safety data base. The concern could arise from:

i. Data from animal studies;

ii. Clinical information from other agents with related chemical structures or from a related pharmacologic class;

(3) pharmacokinetic or pharmacodynamic properties known to be associated with such ADEs.

b. Situations in which there is a need to quantitate the occurrence rate of an expected specific low-frequency ADE will require a greater long-term data base. Examples would include situations where a specific serious ADE has been identified in similar

drugs or where a serious event that could represent an alert event is observed in early clinical trials.

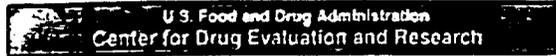
c. Larger safety data bases may be needed to make risk/benefit decisions in situations where the benefit from the drug is either (1) small (e.g., symptomatic improvement in less serious medical conditions) or (2) will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations) or (3) is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint).

d. In situations where there is concern that a drug may add to an already significant background rate of morbidity or mortality, clinical trials may need to be designed with a sufficient number of patients to provide adequate statistical power to detect prespecified increases over the baseline morbidity or mortality.

e. In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small.

8. Filing for approval will usually be possible based on the data from patients treated through 6 months. Data on patients treated through 12 months should be submitted as soon as available and prior to approval in the United States and Japan but may be submitted after approval in the European Union. In the United States, the initial submission for those drugs designated as priority drugs must include the 12 months patient data.

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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.

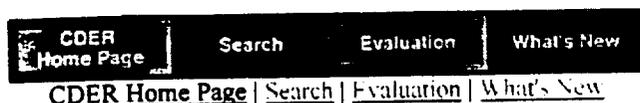
17. ISN'T THE FDA CONCERNED ABOUT THE CRUELTY INFLICTED UPON PREGNANT MARES IN THE MAKING OF PREMARIN?

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.



May 5, 1997
<http://www.fda.gov/cder/ceqa.htm>

Harrington, Jeff, "Duramed Loses Generic Drug Bet, Firm's Future Grim After FDA's Rejection," Cincinnati Enquirer, 5/ 6/97.