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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 10-61
Rockville, MD 20857

Re: Response to Comment, Citizen Petition re: New Drug
Applications for Mixtures of Estrogens, Docket No. 98P-0311

Dear Sir or Madam:

On June 15, 1998, Duramed Pharmaceuticals, Inc. announced that FDA had accepted for filing its new drug application ("NDA") for a five-estrogen product, Cenestin. Duramed had previously developed this product in what became an unsuccessful attempt to obtain approval of an abbreviated new drug application ("ANDA") for a generic version of Premarin® (conjugated estrogens, USP) tablets. Contemporaneous press reports explained that "The FDA's acceptance of the so-called new drug application for Cenestin means Duramed is on track with its latest attempt to market a copycat version of American Home Products Corp.'s blockbuster drug Premarin." (See Exhibits A-C (emphasis added).) As addressed in the Citizen Petition filed in this matter, Duramed is attempting to "end-run" the Center for Drug Evaluation and Research's determination of May 5, 1997 that Duramed's product is not a generic copy of Premarin by filing an NDA supported by only a short-term efficacy study. Duramed's plan is patently illegal and should not be permitted to succeed.

On behalf of Wyeth-Ayerst Laboratories, Division of American Home Products Corporation ("Wyeth-Ayerst"), we submit this response to an August 5, 1998 comment by attorneys for Duramed on the above-referenced Citizen Petition. We also address an additional issue - the impropriety of permitting the Duramed product to be considered as containing a .625 mg dose of estrogens, or to be labeled as such.

Response to Duramed's Comment

Duramed's comment confirms the concerns expressed in Wyeth-Ayerst's Citizen Petition: Duramed is using the NDA route for its five-estrogen product to circumvent the May 5, 1997 decision of the Center for Drug Evaluation and Research ("Center" or "CDER") ("Woodcock Memo") and simultaneously to maximize the likelihood that its product will, if approved, be substituted for Premarin in long-term estrogen therapy,

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including prevention of osteoporosis. Most importantly, the comment all but confirms that Duramed has not undertaken the studies that are required to insure its product's safety for purposes of approval.

We reply to Duramed's arguments below.

1. Reliance on Premarin or Other Estrogen Safety Data to Support Approval of a Five-Estrogen Product Is Improper.

As detailed in the Citizen Petition, even though the content of Duramed's NDA has not been publicly disclosed, the short time frame in which it was prepared and submitted to the Agency suggests that Duramed has not undertaken safety testing required for FDA to approve an NDA for a new drug product containing a novel mixture of estrogenic compounds. While the Duramed comment provides no direct information on this point, it too suggests that, to the extent the NDA offers any safety data at all, Duramed borrows heavily on safety data compiled on Premarin and other estrogen products, notwithstanding differences in estrogenic composition and dosages between those products and Duramed's. In particular, the comment asserts that "FDA commonly considers information available to it with respect to other drugs containing the same ingredients as the subject of an NDA in evaluating safety." (Duramed Comment at 2; emphasis added.) Thus, Duramed apparently is basing a critical aspect of its NDA on the premise that its drug contains the same active ingredient as Premarin – the exact issue decided against Duramed in May 1997 when the Center declined to approve the Duramed ANDA. For the reasons outlined below, the FDA's conclusions with respect to active ingredients in the ANDA context likewise preclude Duramed from relying on data from Premarin or other estrogen products to satisfy the requirements for proof of safety to obtain an NDA.

The keystone of new drug regulation under the Federal Food, Drug, and Cosmetic Act ("FDCA") is the requirement that anyone who wants to market a new drug product must first obtain the FDA's approval by demonstrating that the product is both safe and effective for its intended uses. In general, this may be done either by satisfying the full evidentiary requirements for an NDA under section 505(b) of the Act, or by showing that the new product qualifies for an ANDA because it is bioequivalent to a previously-approved product with the same active ingredients. In the latter case it is presumed that the established safety and effectiveness of the original product can reliably be extrapolated to the new product without the need of duplicative testing. In Duramed's case, however, the FDA has already determined that an ANDA is inappropriate because there is inadequate evidence that the product's active ingredients are the same as

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Premarin's. Therefore, neither its safety or effectiveness can be assumed on the basis of information on the safety or effectiveness of Premarin.

a. Duramed Cannot Satisfy the Requirements for Approval of a Full NDA

Apart from the obvious procedural consequences of FDA's decision – requiring Duramed to seek approval of its product through an NDA instead of an ANDA – FDA's determination that Duramed's five-estrogen combination does not have the same active ingredients as Premarin also has important consequences for the content of Duramed's NDA. Specifically, Duramed cannot satisfy its burden of proving that its novel mixture of estrogens, which is not the same as that of any other product, is safe by relying on (i.e., extrapolating from) safety data compiled on Premarin (or other products), when FDA has explicitly concluded that the effects of such differences on product safety are not known.¹

Among other requirements, section 505(b)(1) of the Act requires NDA applicants to provide “full reports of investigations which have been made to show whether or not such drug is safe for use and . . . effective in use.” (Emphasis added.) Studies of Premarin are, of course, not investigations which have been made to show whether or not a five-estrogen product is safe or effective. Section 505(d)(1) elaborates on this requirement by directing FDA to refuse to approve any application in which the reports of investigations submitted do not include “tests by all methods reasonably applicable to show whether or not such drug is safe” for its intended uses.

As pointed out in the Petition, it appears implausible that Duramed has conducted and submitted its own studies to demonstrate that its product is safe, nor are we aware of any published studies that specifically address the safety of Duramed's five-estrogen product.² Information concerning drugs other than the product covered by the NDA (e.g.,

¹ See Woodcock Memo at 26-27 (“[I]t 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.”).

² Duramed recently announced that it has filed an IND to study the effects of medroxyprogesterone acetate (MPA) administered cyclically in combination with its five-component estrogen product for vasomotor symptoms. This study reflects precisely the kind of safety data, though by no means all of the safety data, that should have been provided in the Duramed NDA from the outset and should be completed prior to any approval. Current medical practice dictates that any estrogen-based product for the treatment of vasomotor symptoms of menopause will be prescribed with concomitant progestin therapy for most women with a

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data on the safety of Premarin or other marketed estrogen drugs) cannot satisfy the statutory requirement that an NDA contain “adequate tests by all methods reasonably applicable to show whether or not [the product]. . . is safe for use[.]” *Id.* We recognize that FDA regulates approved estrogen products as a class in some respects, as by establishing consumer and professional labeling through the framework of labeling guidances. While such an approach may be appropriate when FDA is dealing with common issues among approved estrogen products, each NDA for a novel estrogen mixture must qualify for approval based on its own merits.³

Nor can there be any scientific basis to extrapolate FDA’s conclusions about the safety of Premarin or other products to Duramed’s novel combination of estrogens, in light of FDA’s findings that different estrogen compositions can have potentially profound differences in effects on various body tissues.⁴ To the contrary, the same scientific conclusions that barred Duramed from obtaining an ANDA because its active ingredient was not “the same” as Premarin’s likewise preclude Duramed from relying on studies of Premarin or other different products as proof that the Duramed product is safe.

b. Similarly, Duramed’s Product Does Not Satisfy the Requirements for a “Hybrid” Application

FDA’s so-called “hybrid application” regulation also stops far short of permitting Duramed to rely on data or conclusions concerning Premarin’s safety to satisfy its burden of proof of safety under section 505(b). Under that regulation, an applicant seeking approval of a drug that “represents a modification of a listed drug (e.g., a new indication or new dosage form)” may file an application that “contain[s] only that information needed to support the modifications,” while otherwise relying on FDA’s “finding of safety and effectiveness” for the previously approved drug product. 21 C.F.R. § 314.54.⁵

uterus, and practicing physicians will expect the Duramed product to have already been demonstrated as safe and effective when prescribed in this manner. This forcefully demonstrates the underlying basis of our Petition, which is that the safety and efficacy data package for the Duramed NDA does not support the indications for which the product will be labelled and used.

³ It is well known that numerous preexisting estrogen products were approved for effectiveness as a class under the DESI review. However, the review and the approval practices employed under DESI do not apply to new products first submitted for approval in 1997.

⁴ See, e.g., Woodcock Memo at 9-12, 16, 19-20; and see Petition at 4-5.

⁵ A “hybrid” application is subject to the restrictions set out in FDCA Section 505(b)(2). Section 505(b)(2) was intended to assure that applicants who filed “paper NDAs” would be subject to the same patent and exclusivity restrictions that are applicable to ANDAs. Under FDA’s previous “paper NDA”

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A drug product containing a novel five-estrogen mixture does not represent a "modification" of Premarin or any other approved estrogen product, but is rather an entirely new and different drug product.⁶ In this case, Duramed is still required to provide additional safety "information to support the modification," rather than relying solely on existing safety data on other, different drugs.

Most importantly, FDA has made it clear that the regulation's reference to reliance on earlier safety/efficacy findings applies only "to the extent that such reliance would be allowed under section 505(j) of the act: to establish the safety and effectiveness of the underlying drug."⁷ Because FDA has concluded that Premarin cannot serve as the basis for ANDA approval of products having these specific mixtures of estrogenic compounds, such compounds cannot be approved under NDAs submitted pursuant to 21 C.F.R. § 314.54.

Duramed thus may not rely on FDA's conclusions that Premarin or other estrogen drugs are safe to avoid conducting the full complement of safety testing required to obtain an NDA because (1) there is no statutory authorization for Duramed to rely on

policy, certain NDAs for generic duplicates of drugs first approved after 1962 (which were not then eligible for ANDAs) were permitted to rely on scientific literature reports on the pioneer product. The requirement of identical active ingredients was – and remains – critical to the logic of this policy. *See, e.g.*, 45 Fed. Reg. 82,052, 82,052 (Dec. 12, 1980) ("[W]hen it is well established in the literature that a drug is safe and effective for a particular use . . . there is no valid scientific reason to require more tests in animals and humans to show that the same drug is safe and effective for the same use.") (emphasis added). FDA has repeatedly emphasized that section 505(b)(2) applications "are submitted under section 505(b)(1) of the act . . . [and] are therefore subject to the same statutory provisions that govern full new drug applications." 54 Fed. Reg. 28,872, 28,875 (July 10, 1989) (preamble to proposed ANDA regulation); 57 Fed. Reg. 17,950, 17,952 (April 28, 1992) (preamble to final ANDA regulation).

⁶ In this regard, note also that FDA's examples of products eligible for NDA approval under 21 C.F.R. § 314.54 (i.e., new indication or new dosage form) presume that the active ingredient remains unchanged.

⁷ 54 Fed. Reg. 28,872, 28,892 (July 10, 1989) (preamble to proposed ANDA implementation rule). As explained in the preamble, this provision was designed to streamline the application process for products that are sufficiently different from a reference listed drug to require additional investigations to confirm that the modified version is safe and effective (and therefore could not be directly approved under an ANDA), but that *could be approved by first obtaining an ANDA to duplicate the listed drug*, then filing a supplemental NDA to cover the modification. Even though FDA has eliminated the intermediate step of obtaining an ANDA, it clearly views eligibility for an ANDA as a critical prerequisite for reliance on safety findings concerning another drug to substitute for actual safety testing. CDER has made it clear that the Duramed product is not eligible for an ANDA.

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data in the Premarin (or any other estrogen) NDA, and (2) as FDA has already found, the information about Premarin's safety cannot be extrapolated to a five-estrogen product.

2. Revocation of Current USP Monographs

As CDER's analysis concerning the composition of conjugated estrogens demonstrates, the current United States Pharmacopeia ("USP") monographs for conjugated estrogens and conjugated estrogens tablets are incorrect. The five components identified in these monographs as being required components reflect the composition of no marketed drug product. They are simply a collection of estrogens with no obvious justification.

Duramed argues that no action be taken with respect to the monographs until the completion of its appeal of the Center's position. Such a delay would do no harm were it not for the pendency of the Duramed NDA. If there were an approval of such a product, however, it would be entirely inappropriate to have the five-estrogen product viewed as complying with the conjugated estrogens monographs. This is because the monograph improperly, by implication, validates the composition of such a product as comprising "conjugated estrogens." After all, FDA's position, and the theory behind the submission of an NDA rather than an ANDA for the product, is that the five-estrogen product is not conjugated estrogens. Accordingly, should FDA actively consider approval of a five-estrogen NDA, it should take appropriate steps to assure withdrawal of the USP monographs prior to marketing of such a product.

3. The Name of the Duramed Product Should Not Include "Conjugated" in Conjunction with "Estrogens"

Duramed argues that a prohibition on the use of the terms "conjugated" and "estrogens" in the name of its product would be inappropriate because that product contains estrogens that are conjugated. The comment does not address the obvious point that physicians and patients would be led to believe that Duramed's product was equivalent in estrogen composition to Premarin if both contain the identical generic name in their labeling. Moreover, there are synonyms for the word "conjugated" that are equally descriptive and that would not mislead the public into believing that the five-estrogen product is the same as conjugated estrogens. For example, the term "sulfated" would be even more descriptive than "conjugated" to describe the Duramed estrogens and would avoid confusion with Premarin. If Duramed's NDA is approved, therefore, Duramed should not be permitted to refer to its product as "conjugated" estrogens.

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4. Any Duramed Product Must Be Clearly Labeled
and Promoted as Not Substitutable for Premarin

Contrary to Duramed's comment, FDA has ample authority to require that the labeling of any five-estrogen product clearly state that that product differs from conjugated estrogens. The examples cited in the Petition illustrate this. See Petition at 10-11, fn. 4. The statutory authority for such a requirement is FDCA Section 505(d)(7), which requires refusal to approve an NDA if "based on a fair evaluation of all material facts, [the drug's] labeling is false or misleading in any particular; . . ." See also 21 C.F.R. § 314.125(b)(6) (to the same effect). The failure to incorporate such a statement in labeling or advertising would be misleading because "the labeling or advertising [would fail] to reveal facts material in the light of . . . representations" made in the labeling or advertising, FDCA Section 201(n). In this case, the failure to reveal that the five-estrogen product is not the same as, and thus is not substitutable for, Premarin would clearly be misleading, and would thus be a basis for refusal to approve the NDA for that product. Similarly, if the NDA were approved, promotional statements that did not reveal the difference between the products, in light of the history of Duramed's repeated and well-publicized assertions that its product is the same as Premarin, would constitute misbranding as false and misleading statements pursuant to FDCA Sections 502(a) and 201(n).

Indeed, the fact that the Duramed comment states that its product may be substituted for Premarin for vasomotor indications highlights the need for such a prominent and candid disclosure. If the Duramed product were approved to treat vasomotor symptoms, a physician could decide to prescribe that product instead of Premarin for those symptoms. However, that decision should be based on a clear understanding that the two products are not equivalent and that the Duramed product has neither been demonstrated to provide Premarin's benefits in the prevention of osteoporosis nor has it been shown to be appropriate for long-term use. In addition, it must be made clear through the use of affirmative statements that the Duramed product is not a generic version of Premarin that may be substituted at the pharmacist level.

Duramed's Product Cannot Be Labeled as .625 mg.

The fact that Duramed intends that its product will be substituted for Premarin is also apparent from the fact that Duramed is asking that its product be labeled with a strength of .625 mg. There is absolutely no legal basis for such a label claim. The Duramed product was designed to contain five of the estrogens in Premarin and, as such, its total estrogen content is approximately .7 mg. That is the total that should appear on the Duramed product's label.

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We recognize that the total estrogen content of the Premarin tablet labeled as .625 mg is also much higher than .625 mg. Wyeth-Ayerst has in the past discussed with FDA this label claim. FDA has taken the position, with which we agree, that this label claim should be retained for Premarin, as it is for other estrogens historically so labeled, such as esterified estrogens, to avoid consumer confusion that would result if the same product that has been marketed for decades as a .625 mg tablet should be relabeled without any change in content.

On the other hand, a .625 mg label claim for the Duramed product would create professional and consumer confusion that the Duramed product is substitutable for Premarin. The fact that Duramed is seeking such labeling is, we believe, direct evidence of its intent to market its product as a Premarin substitute. There is, therefore, no justification to permit a .625 mg label claim for the Duramed product or any other five-estrogen product.

Thus, if the Duramed product (or an NDA for the Barr ANDA formulation) is approved, FDA must at a very minimum assure that it is labeled in compliance with section 502(b)(2) and thus does not carry a .625 mg label claim.⁸

⁸ Petitioners believe it is appropriate to raise this point in the context of discussion of the pending petition. If, however, FDA believes that this additional request for relief should be considered an amendment of the original petition, petitioners request that it be so considered.

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Accordingly, for the reasons stated herein and in the Petition itself, the Wyeth-Ayerst Petition should be granted.

Respectfully submitted,



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