DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 24, 1999

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Re: Docket No. 98P-0311/CP1

Dear Mr. Land, Mr. Beers, Mr. Korn, and Ms. Buc:

This letter responds to your citizen petition dated May 12, 1998, filed on behalf of Wyeth-Ayerst Laboratories, Division of American Home Products Corporation (Wyeth-Ayerst). Wyeth-Ayerst is the manufacturer of Premarin conjugated estrogens tablets. Your petition requests that the Food and Drug Administration (FDA) deny approval of any new drug application (NDA) for a mixture of five of the estrogens found in Premarin in the absence of safety and effectiveness testing of the type required for any new chemical entity. Specifically, you request that:

1. FDA require full compliance with NDA safety and effectiveness requirements,
2. FDA seek revocation of the current United States Pharmacopeia (USP) monographs for conjugated estrogens and conjugated estrogens tablets,
3. if NDA approval of any such drug product is permitted, *conjugated estrogens* not be included in any part of the name, and
4. if NDA approval of any such drug product is permitted, any labeling and marketing materials associated with such a drug product state that the drug product is not equivalent to or substitutable for Premarin.

FDA has considered information submitted in your petition, as well as comments made by Wyeth-Ayerst's representatives at a meeting with representatives of the Center for Drug Evaluation and Research (CDER) on November 5, 1998, comments filed by Duramed Pharmaceuticals, Inc. (Duramed), dated August 5, 1998, and your response to Duramed's comments dated January 7, 1999. For the reasons explained below, your petition is denied.

98P-0311 PDN1

I. Safety and Effectiveness of NDAs for Synthetic Conjugated Estrogens Drug Products

You request that FDA recognize that sponsors of any NDA for a multiple-ingredient synthetic conjugated estrogens drug product cannot satisfy the requirements of section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)) to demonstrate the safety and effectiveness of their product by relying on animal and human clinical studies of other estrogens, including 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 (Petition at 3).

A new drug may be approved if the applicant provides adequate evidence demonstrating the drug's safety and effectiveness as required by the Act. Section 505(b)(1)(A) of the Act requires an NDA to contain "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." An application described in section 505(b)(2) is submitted under section 505(b)(1) and is thus required to contain adequate evidence of safety and effectiveness. However, a 505(b)(2) application may rely for approval upon investigations that were not conducted by or for the 505(b)(2) applicant and to which the applicant has not obtained a right of reference. The data to support the safety and/or effectiveness of the drug product in the 505(b)(2) application may be derived wholly, or in part, from published reports of studies conducted by someone other than the applicant or from a prior Agency finding of safety and effectiveness of the drug.

A. Safety Data

As you know, Duramed has submitted for approval an NDA for a synthetic conjugated estrogens drug product under section 505(b)(2) of the Act. This application included a 3-month safety and efficacy study in humans conducted by Duramed on Cenestin. This study was a randomized, double-blind, placebo-controlled, dose-titration clinical trial in 120 healthy adult menopausal women. The study consisted of three distinct periods: a screening period during which patients were screened to determine eligibility, a 2-week baseline period during which predose hot flashes and nocturnal sweating were measured to qualify the patient for the study, and a 12-week treatment period. Standard evaluations performed during the screening period and at the end of the study, or as soon as possible after discontinuation, included a general physical examination, a gynecologic examination with pelvic examination, a Pap smear and pregnancy test, and laboratory evaluations. Laboratory tests obtained included: liver function tests, lipid tests (HDL and LDL cholesterol), hematology (red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count and differential, and platelets), and biochemistry (glucose, urea, total protein, albumin, creatinine, uric acid, sodium, potassium, calcium, and alkaline phosphate). During the treatment period, study participants were seen eight times: at the first dose, and during weeks 1, 2, 4, 6, 8, 10, and 12. Additional visits were scheduled to monitor

any adverse event or premature withdrawal from the study. During these visits, vital signs of the participants were taken, including systolic and diastolic blood pressure, pulse rate, and weight. No deaths or serious adverse events were reported during this 3-month study. CDER thoroughly reviewed the data from this study and concluded that these data supported the conclusion that Duramed's synthetic conjugated estrogens drug product is safe for short-term use in humans.

Animal safety data on estrogens, either in vitro or in vivo, have not proven to be quantitatively predictive of the effects of these products in women.[1] The most confident conclusions can be drawn from experience in humans. Animal data is designed as a screen to identify gross toxicities, such as whether or not a drug product is a potential human carcinogen. Animal tests cannot be used to definitively assign human clinical effects, but they are useful in screening compounds for activity. There is extensive animal safety data available in the published literature on estrogens. Conjugated estrogens and estrogens in general have been the subject of substantial toxicological evaluation.[2] Safety studies in humans, animals, and in vitro have examined the mechanism of action of estrogens, their binding to estrogen receptors, activation of estrogen response elements, metabolism, pharmacokinetics, and relative potencies. It is known from both animal and, more importantly, human data that estrogens are carcinogenic. Because of the volume of available data on estrogens, CDER does not require new safety studies in animals prior to testing in humans or prior to drug product approval. For example, no long-term animal safety testing has been required for any of the estrogen-alone products for menopausal therapy approved through the NDA or abbreviated new drug application (ANDA) process. Estrace (estradiol tablets) was approved in 1975 and Ogen (estropipate tablets) in 1977 through the ANDA process and thus were not required to provide animal safety data. Several transdermal estradiol delivery systems and one vaginal estradiol delivery product were approved through the NDA process since Premarin's approval in 1942. Although short-term animal safety data relevant to the delivery systems were included in these applications, no new long-term animal safety studies were required for those approvals. As is the case with other approved drug products in this class, existing animal safety data for estrogens are appropriately extrapolated to new estrogen drug products, including Duramed's synthetic conjugated estrogens drug product.

You state that a product containing only some of the estrogens in Premarin could be unsafe because the estrogens not included may provide a protective effect or may compete as antiestrogens for estrogen receptors with estrogens that might otherwise cause adverse effects (Petition at 4). In support of your position, you cite a statement made in CDER's May 5, 1997,

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[1] Stern, M.D., "Pharmacology of Conjugated Oestrogens," *Maturitas*, 4:285-290, 1982.

[2] Westerholm, B., "Clinical Toxicology of Estrogens," *Pharmacol. Ther.*, 10:337-349, 1980.
Hart, J.E., "Endocrine Pathology of Estrogens: Species Differences," *Pharmacol. Ther.*, 14:203-218, 1990.

memo (CDER memo),[3] that

> 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. (CDER memo at 19)

While it is true that changing the concentration of binding proteins could change the concentration of free steroids in the bloodstream and therefore make Premarin more or less potent, estrogenic potency is more relevant to clinical efficacy, which cannot be evaluated in animal studies. Duramed has conducted a dose-titration clinical trial in humans to establish the safety and efficacy of its drug product. Safe and effective dosage and administration for the product has been determined as a result of this trial. As an NDA, Duramed is not required to do comparative trials to Premarin. Duramed's synthetic conjugated estrogens drug product has been determined on the basis of clinical data to be safe and effective at the dosage strengths approved.

Your petition states that any newly approved synthetic conjugated estrogens drug product approved for the vasomotor symptom indication will inevitably be used in chronic estrogen replacement therapy, such as the prevention of osteoporosis. You state that Premarin has been shown to be safe for such chronic use (Petition at 6).

One of the principal preclinical testing requirements for a drug product used chronically is a carcinogenicity study. The issue of potential carcinogencity has been addressed for conjugated estrogens, including Premarin. In June 1998, the International Agency for Research on Cancer (IARC) met in Lyon, France, to consider the carcinogenicity of postmenopausal estrogen therapies. After considering the published data on studies in animals and humans, the IARC stated that there is sufficient evidence in human studies for the carcinogenicity of

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[3] On May 5, 1997, in accordance with 21 CFR 314.120, CDER notified Duramed and Barr Laboratories, Inc., that their respective ANDAs for synthetic conjugated estrogens tablets were not approvable under sections 505(j)(2)(A)(ii)(II) and 505(j)(3)(C)(ii) of the Act because both ANDAs were insufficient to show that the active ingredients of their proposed generic drug products were the same as the active ingredients of the reference listed drug, Premarin. CDER attached a detailed memorandum to the not approvable letters. This memo, from the CDER Director to the Director of the Office of Generic Drugs, outlined the legal and scientific rationale for CDER's position that a synthetic generic version of Premarin cannot be approved until the active ingredients of Premarin have been sufficiently well defined to permit an ANDA applicant to show that a synthetic generic form of Premarin has the same active ingredients as Premarin.

postmenopausal estrogen therapy.[4]

Evidence of the carcinogenicity of conjugated estrogens came from two papers based on studies in hamsters with hydrolyzed Premarin, equilin and d-equilenin, and estrone.[5] Both studies found that conjugated estrogens are carcinogenic. In one of the studies, Premarin produced tumors in 100 percent of the animals tested; clearly there was no protective effect of Premarin. Further animal testing of individual estrogens would not change this estimation of human health risk.

You also suggest that the Agency should require clinical studies of synthetic conjugated estrogens drug products sufficient to demonstrate their long-term clinical safety. You cite an International Conference on Harmonization (ICH) guidance, which you state "require[s] 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 1-year exposure to support a determination of safety" (Petition at 6, citing ICH E1A, *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*, 1995, p. 3). At this time, however, Duramed's synthetic conjugated estrogens drug product is being approved only for treatment of vasomotor symptoms associated with menopause, and not for long-term treatment for indications such as osteoporosis. Therefore, CDER is not requiring data on long-term safety at this time.[6] Furthermore, any sponsor who wishes to demonstrate that its product has superior long-term safety compared to any other product will be required to do comparative human trials.

In your comments filed on January 7, 1999, you assert that the Agency should require Duramed to complete a clinical study on the use of progestin in combination with Duramed's synthetic conjugated estrogens drug product prior to approval (1/7/99 Response to Comment at 3, footnote 2). Any estrogen drug product approved for the treatment of vasomotor symptoms associated with menopause will be required to carry the class labeling for non-contraceptive estrogen drug

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[4] IARC, "Some Hormones, Postmenopausal Hormone Therapy, and Hormonal Contraception," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* 72: in preparation, June 2-9, 1998. Available on the IARC website at: http://193.51164.11/htdocs/announcements/vol.72.htm.

[5] Li, J.J., S.A. Li, J.K. Klicka, J.A. Parsons, and L.K.T. Lam, "Relative Carcinogenic Activity of Various Synthetic and Natural Estrogens in the Syrian Hamster Kidney," *Cancer Research,* 43:5200-5205, 1983.
Li, J.J., S.A. Li, T.D. Oberley, and J.A. Parsons, "Carcinogenic Activities of Various Steroidal and Nonsteroidal Estrogens in the Hamster Kidney: Relation to Hormonal Activity and Cell Proliferation," *Cancer Research,* 55:4347-4351, 1995.

[6] Unlike Cenestin, Activelle and Levlite (two examples raised in the correspondence filed in the docket) both contain estrogen and progestin for long-term hormone replacement therapy and oral contraception, respectively. Long-term clinical trials were required for these products because of their long-term indications.

products.[7] This labeling includes the discussion of the addition of a progestin to an estrogen replacement therapy. CDER does not require the completion of a clinical study on the use of progestin and an estrogen drug product unless the estrogen drug product is marketed in combination with progestin. Duramed has not indicated any intent to market its product in combination with progestin. Because its product is being approved for the treatment of vasomotor symptoms associated with menopause, Duramed's synthetic conjugated estrogens drug product will carry the class labeling for such drug products.

In sum, the human clinical safety data on Duramed's synthetic conjugated estrogens drug product and the extensive published literature on the clinical effects of estrogen, as well as on estrogen toxicology, specifically on carcinogenicity, lead CDER to conclude that additional safety studies are not needed or appropriate to support the safety of this drug product. For the above reasons, your request that FDA refuse to approve any NDA for a synthetic conjugated estrogens drug product relying on animal and human clinical studies of other estrogens, including conjugated estrogens, to demonstrate safety is denied.

B. Effectiveness Data

You state that any approved NDA for a synthetic conjugated estrogens drug product should be required to substantiate effectiveness on the basis of its own particular composition (Petition at 4). As previously stated, in the case of the synthetic conjugated estrogens drug product sponsored by Duramed, the sponsor conducted a pivotal double-blind, placebo-controlled, dose-titration study in 120 menopausal women. This study was conducted to determine the effectiveness of specific dosage strengths of the drug product after 12 weeks of treatment of moderate to severe vasomotor symptoms. The Agency reviewed the results of this clinical trial and, based on a thorough analysis of the data submitted, determined that Duramed had substantiated the effectiveness of their synthetic conjugated estrogens drug product in an appropriately designed clinical trial. FDA will determine on a case-by-case basis whether to require such studies in 505(b)(2) applications for synthetic conjugated estrogens drug products in the future, based on an assessment of the particular estrogens proposed for the drug product.[8] Therefore, the Agency denies your request that any approved NDA for a synthetic conjugated estrogens drug product be required to substantiate effectiveness on the basis of its own particular composition.

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[7] CDER recently proposed changes to its labeling guidance for non-contraceptive estrogen drug products, which may affect the class labeling for estrogen drug products. See FDA's draft guidance for industry, *Labeling Guidance for Non-Contraceptive Estrogen Drug Products — Physician and Patient Labeling*, 1998.

[8] See FDA's guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*, 1998.

II. Status of USP Monographs for Conjugated Estrogens

You request that FDA seek revocation of the current USP monographs for conjugated estrogens and conjugated estrogens tablets (Petition at 8). You state that the current USP monographs for those products are inaccurate and based on inadequate data. You raise concerns that the monographs will inappropriately validate any synthetic conjugated estrogens drug product and mistakenly foster the inference that any such product is the same as Premarin. To support your argument, you cite statements made by CDER in denying approval of ANDAs for such products.

Under section 505(j)(2)(A)(ii)(II) of the Act, an ANDA for a drug product with more than a single ingredient must include information to show that the active ingredients of the drug that is the subject of the ANDA are the same as those of the reference listed drug, except for any different active ingredient for which a petition was approved under section 505(j)(2)(C) of the Act. After much consideration, the Agency determined in 1997 that it could not at that time approve an ANDA based on Premarin because the ANDA applications failed to provide sufficient information to show that the active ingredients of these synthetic conjugated estrogens drug products were the same as the active ingredients of the reference listed drug product, Premarin (62 FR 42562 at 42572, Aug. 7, 1997). CDER determined that Premarin was not adequately characterized and, therefore, the active ingredients could not be defined sufficiently to determine sameness. In support of its decision, CDER made available on its website a list of anticipated questions concerning this decision, along with CDER's answers (*Synthetic Conjugated Estrogens: May 5, 1997 Questions and Answers*). CDER provided a detailed statement concerning new scientific information on estrogens and improved techniques for compositional analysis. CDER stated that, on the basis of the new information and improved techniques, it could no longer support the position taken in the current USP monograph. In response to the question "What will happen to the USP monograph for conjugated estrogens?" CDER stated that it was considering making recommendations to the USP in light of current scientific information about the composition of conjugated estrogens.

On June 9, 1997, CDER sent a letter to the USP reiterating the findings in the CDER memo and stating that CDER would provide the USP with a revised definition of conjugated estrogens as soon as it was established. Since that time, CDER's Division of Testing and Applied Analytical Development has been working both on its own and in cooperation with Wyeth-Ayerst to fully characterize Premarin. As you know, this goal has not yet been achieved. CDER is still considering whether the current conjugated estrogens monographs should be withdrawn or only modified, and awaits the results of Wyeth-Ayerst's full characterization of Premarin.

Furthermore, any synthetic conjugated estrogens drug product will not be labeled "USP" until such time as a drug monograph for synthetic conjugated estrogens is adopted. The current USP drug monographs for conjugated estrogens do not apply to Duramed's synthetic conjugated estrogens drug product.

In sum, at this time the Agency does not intend to request that the USP withdraw its current monographs for conjugated estrogens. When the Agency has the data it needs regarding a full characterization of Premarin, it will decide whether to work with the USP to revise the conjugated estrogens monographs or to request that the USP withdraw the existing monographs. Therefore, your request that FDA seek immediate revocation of the current monographs is denied.

III. Name of A New Synthetic Conjugated Estrogens Drug Product

You request that if a new synthetic conjugated estrogens drug product is approved, it bear a different common or usual name than Premarin. You request that *conjugated estrogens* not be used in the name of any such new drug product. You claim that because any such product would be chemically and compositionally different from Premarin, confusion would result from the use of this term in the name of any newly approved drug product. You suggest that a descriptive, yet distinct, name for any such product should be selected, and you propose the name "synthetic sulfated estrogen mixture" (Petition at 8-9).

While FDA has the statutory authority under section 508 of the Act (21 U.S.C 358) to designate an official name for any drug product, the Agency does not routinely designate official names. Section 502(e) of the Act (21 U.S.C. 352(e)) prescribes that the labeling of a drug must bear its established name, if there is one, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula). Section 502(e)(3) of the Act defines the term *established name* as the *common or usual name*, unless that name is superseded by an *official name* designated by FDA or, if there is no such official name designated, the common or usual name may be superseded by the *official title* if one has been designated in an official compendium. Because FDA does not routinely designate official names under section 508 of the Act, current Agency regulations (21 CFR 299.4(e)) provide that, in the absence of such designation, the established name will be the compendial name or the common or usual name, both of which are provided in the *USAN (United States Adopted Name) and the USP Dictionary of Drug Names*.[9] Section 299.4(d) of the CFR incorporates by reference the guiding principles for coining U.S. adopted names. These principles state that a "nonproprietary name

[9] The current name of the publication is the *USP Dictionary of USAN and International Drug Names* (1998). This publication includes the U.S. Adopted Name (USAN), the compendial name, and/or the common or usual name.

should be useful primarily to health practitioners . . . for use in the routine processes of prescribing, ordering, dispensing, and administering drugs throughout the United States" ("Guiding Principles for Coining U.S. Adopted Names," reprinted in *USP Dictionary of USAN and International Drug Names,* 35th ed., 1998).

The Agency has carefully considered possible names for any new synthetic conjugated estrogens drug products and proposes that the choice most consistent with the naming principles outlined above is *synthetic conjugated estrogens*. The nonproprietary name of the first such product approved will be *synthetic conjugated estrogens, A*. Any subsequently approved new drugs in the same class would be named consecutively and in alphabetical order: *synthetic conjugated estrogens, B, C, D,* and so on. The word *synthetic* appears first in the name to inform the practitioner that the product is derived through both chemical extraction and chemical modification processes. Although the ingredients of a synthetic conjugated estrogens product are chemically well-characterized, other conjugated estrogens products derived from natural source materials, such as Premarin, contain additional steroidal components. Therefore, it is useful to make a clear distinction between synthetic and nonsynthetic drug products.

The Agency has determined that *conjugated estrogens* is the best descriptive term for this class of synthetic drug products. When the nonproprietary name of *conjugated estrogens* was selected for Premarin, it was based on sulfated ester forms of estrogen components. We now know that Premarin contains other ester forms, glucuronides, and doubly-sulfated forms, which are not clearly defined. For products with some or all of the major components as Premarin, in the same proportions as Premarin, the use of the same nonproprietary name chosen for Premarin as part of the new products' nonproprietary name is entirely appropriate.

The use of the isolated letter *A* at the end of the phrase *synthetic conjugated estrogens* fulfills the clear purpose of distinguishing differing compositions of synthetic conjugated estrogens that may be approved in the future. CDER anticipates that the term *synthetic conjugated estrogens* will apply to a class of drug products best identified by that term, but with a need to distinguish possible future differences between subsequent synthetic conjugated estrogens drug products. Any such drug product that is approved subsequent to the first will receive a consecutive alphabetical designation, preceded by a comma, to convey the necessary distinction.

You assert that Premarin is *conjugated estrogens* and has been marketed under that name for more than half a century. However, this confuses the nature of a nonproprietary, common, or usual name with that of a proprietary name. Certainly Premarin, as a proprietary name, is for your exclusive use. However, *conjugated estrogens* is a nonproprietary name and in the public domain. In fact, as you know, 28 other conjugated estrogens drug products were marketed under that name until they were withdrawn from the market in 1991, after the Agency's determination usual name.

could no longer be considered safe and effective.[10] For the reasons discussed above, the Agency has determined that the use of *synthetic conjugated estrogens* is the clearest and most reasonable choice for the common or usual name of this new product. Therefore, your request that any new synthetic conjugated estrogens drug product bear a different common or usual name than Premarin, and that *conjugated estrogens* not be used in the name of any such product, is denied.

IV. Restrictions on Marketing Materials

You request that any NDA approval of a synthetic conjugated estrogens drug product be conditioned upon disclosures, in all labeling and promotional materials, that the drug product is not equivalent to and should not be substituted for Premarin (Petition at 9).

The Agency's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) will not state that a synthetic conjugated estrogens drug product is therapeutically equivalent to Premarin. The Orange Book contains information on drug products approved on the basis of safety and effectiveness by FDA and includes their therapeutic equivalence (TE) codes. Drug products are considered to be therapeutic equivalents if they are both pharmaceutical equivalents, and if they can be expected to have the same clinical effect and safety profile when used under the conditions specified in the labeling. The Orange Book is the public's main source of information about the equivalence or substitutability of drug products. The Orange Book identifies a reference listed drug, which is the drug product upon which an ANDA applicant will rely in seeking approval of its application. Generic drugs are listed with TE codes to indicate their equivalence or substitutability with respect to the listed drug. As previously discussed, CDER made an initial decision to refuse to approve generic synthetic conjugated estrogens drug products using Premarin as the reference listed drug because of uncertainty as to the identity of the active ingredients.[11] A synthetic conjugated estrogens drug product containing different active ingredients than Premarin will not be listed in the same active ingredient subsection of the Orange Book as Premarin and thus could not be listed as equivalent to Premarin. It will be listed as a reference listed drug (21 CFR 314.94(a)(3)) in the Orange Book, and will have no therapeutic equivalence rating unless and until the Agency approves another drug with the same active ingredients, dosage form, and strength. Because the first synthetic conjugated estrogens drug product will not be listed with a TE code and will be listed in a different active ingredient subsection, there would be no basis to conclude that such drug

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[10] See 56 FR 12376, March 25, 1991.

[11] See footnote 3. In response to the Agency's notice of opportunity for a hearing (62 FR 42562, Aug. 7, 1997) on the denial of approval of Duramed's and Barr's ANDAs for conjugated estrogens tablets, both companies requested a hearing. Final Agency action on this matter is under review pursuant to 21 CFR 314.200(g).

product is substitutable for Premarin.[12] Please note, however, that estrogen replacement therapy occurs under a physician's guidance, and thus the physician retains discretion in the choice of which drug product to prescribe for such therapy.

You suggest that public statements made by Duramed in response to FDA's denial of Duramed's ANDA for a synthetic conjugated estrogens drug product provide an appropriate context for CDER to require clear statements in all labeling and promotional materials indicating that Duramed's product is not equivalent to or substitutable for Premarin (Petition at 10). You state that these earlier statements indicate that Duramed may make misleading statements to benefit the sales of any approved NDA for a synthetic conjugated estrogens drug product. To support your argument, you state that FDA has the authority to require labeling for differences between drugs that might be substituted for each other, and you cite the examples of an insulin drug product and an interferon drug product. The Agency does not agree with your conclusion that the statements Duramed made in relation to the Agency's denial of approval of its ANDA or that Duramed may have made in advance of approval of its NDA, should influence labeling decisions for any new synthetic conjugated estrogens drug product.

Section 505(b)(1) of the Act and 21 CFR 314.50(e)(2)(ii) require that an NDA sponsor include specimens of the labeling proposed to be used for the new drug, and require copies of all labels and labeling to be submitted to FDA. CDER's Division of Drug Marketing, Advertising, and Communications reviews promotional materials for a newly approved drug product to ensure compliance with labeling requirements under 21 CFR 314.81(b)(3), and it regulates prescription drug advertising under section 502(n) of the Act and under 21 CFR part 202 of the corresponding regulations.

FDA relies on the misbranding provisions of the Act and its corresponding regulations to enforce any false or misleading statements manufacturers make when marketing a new drug. Section 502(a) of the Act states that a drug shall be deemed to be misbranded if "its labeling is false or misleading in any particular." Section 201(m) (21 U.S.C. 321(m)) of the Act defines labeling as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Section 201(k) defines the term label as: " a display of written, printed, or graphic matter upon the immediate container of any article . . . ." Failure to comply with these labeling and marketing requirements will trigger the enforcement provisions provided under the Act and corresponding regulations.

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[12] The Orange Book is used by various organizations to make determinations about substitution of drug products (Orange Book at v).

The two drug products you cite as examples of the type of warnings you suggest for synthetic conjugated estrogens drug products are an insulin product, Humulin L, manufactured by Eli Lilly and Company and derived from recombinant DNA techniques, and an interferon[13] product, Roferon-A, manufactured by Roche Laboratories and also derived from recombinant DNA techniques. Both of these drug products are approved for treatment of chronic and serious diseases. Humulin L is used to treat diabetes; Roferon-A is used in immunocompromised individuals to treat diseases such as chronic active hepatitis B, AIDS-related sarcomas, non-Hodgkin's lymphoma, multiple myeloma, and breast and ovarian carcinomas. For both these products, the risk of accidental substitution has the potential to create life-threatening circumstances. No such life-threatening circumstance would be created by the accidental substitution of Premarin for a synthetic conjugated estrogens drug product, or vice versa. Therefore, warnings of the type used on the labeling of Humulin L and Roferon-A are not necessary for synthetic conjugated estrogens drug products.

As you know, the current labeling for non-contraceptive estrogen drug products, including Premarin, contains prominent warning statements that "estrogens have been reported to increase the risk of endometrial carcinoma" and "estrogens should not be used in pregnant women." The first statement is required because the reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. The second statement is required because treatment with diethylstilbestrol (DES), which is an estrogen, during pregnancy has been associated with an increased risk of congenital defects in the reproductive organs of the fetus and possibly other birth defects. Labeling statements also include the warning that close clinical surveillance of all women taking estrogens is important. Further, warnings for non-contraceptive estrogen drug products include induction of malignant neoplasms, gallbladder disease, and effects similar to those caused by estrogen-progestin oral contraceptives, including thromboembolic disease, hepatic adenoma, elevated blood pressure, glucose tolerance, and hypercalcemia. Information for the patient includes the dangers and risks associated with estrogens and suggests that patients, in consultation with their health care practitioners, should decide whether the benefits of usage outweigh the risks. Any approved synthetic conjugated estrogens drug product will be required to carry labeling statements appropriate to non-contraceptive estrogen drug products as a class.[14]

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[13] Interferon drug products are regulated by the Center for Biologics Evaluation and Research (CBER) within FDA.

[14] See footnote 7.

Your comment to the docket filed on January 7, 1999, raises the additional issue that if a synthetic conjugated estrogens drug product is approved, it should not be labeled indicating a 0.625-mg dosage strength. You state that based on your knowledge of the five estrogens in Duramed's product, it has a total estrogen content higher than 0.625 mg. Although you acknowledge that the total estrogen content of Premarin tablets currently labeled as 0.625 mg is much higher than that amount, you state that FDA previously has taken the position, which you support, that the 0.625-mg label claim for Premarin should be maintained to avoid the consumer confusion that would result if Premarin were relabeled. You nevertheless argue that a 0.625-mg label claim for the Duramed product would create professional and consumer confusion that the Duramed product is substitutable for Premarin.

The strengths assigned to Duramed's product (0.625 mg and 0.9 mg) maintain the convention currently in place for labeling of multiple estrogen products. Conjugated estrogens are labeled according to the sum of the three most prevalent components (sodium estrone sulfate, sodium equilin sulfate and sodium 17α-dihydroequilin sulfate) of a multiple component mixture. Esterified estrogens, which are another type of conjugated estrogens product, are labeled according to the sum of the two most prevalent components (sodium estrone sulfate and sodium equilin sulfate) of a multiple component mixture (depending on the product, it may also contain 17α-estradiol and/or 17α-dihydroequilin). Commercially available examples include Estratab and Menest (esterified estrogens tablets, USP), which are available as 0.3, 0.625, 1.25, and 2.5 mg tablets.

Although historically the designation of strength was based on a potency bioassay, as more sophisticated and specific techniques have developed for identifying components, the potency bioassay has been replaced with the current convention (as described above) of measurement of the most prominent ingredients. For conjugated estrogens, the milligram designation determined through the original bioassay measurement correlated to the sum of the three most prevalent components, and thus this system was adopted.

Specifications for Cenestin maintain the convention applied to other conjugated estrogens. The milligram designation is based on the "sum of three" convention in place for other conjugated estrogens with multiple components. The established name in this case encompasses products with multiple components. To apply the convention used in other product classes of naming each ingredient, along with its strength, in either the established name or its description is not practical and would be confusing. In the case of conjugated estrogens, including esterified estrogens, the established name would become a long string of specific estrogen components along with the individual strength of each — an

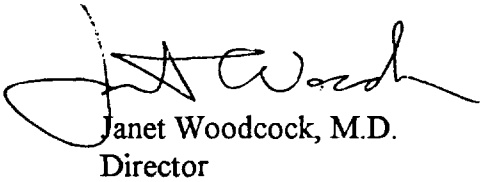
unwieldy, confusing, and impractical labeling solution. Thus, for these multiple component products, CDER will continue the "sum of three" practice for the milligram designation of the conjugated estrogen products.

To date, the Agency has determined that there are no public health or safety issues that require the types of restrictions you suggest for labeling or other promotional materials. Should any such issues develop in the future, FDA will take all appropriate action necessary to protect the public health and safety. Therefore, your request that any NDA approval of a synthetic conjugated estrogens drug product be conditioned upon prominent disclosures that the drug product is not equivalent to or substitutable for Premarin is denied.

V. Conclusion

Your request that FDA refuse to approve any NDA for a synthetic conjugated estrogens drug product relying on animal and human clinical studies of other estrogens, including conjugated estrogens, to demonstrate safety and effectiveness is denied. Your request that FDA seek revocation of the current USP monographs for conjugated estrogens and conjugated estrogens tablets is denied. Your request that the phrase *conjugated estrogens* not be used in the name of any newly approved synthetic conjugated estrogens drug product is denied. Your request that any NDA approval of a synthetic conjugated estrogens drug product be conditioned upon disclosures in all labeling and promotional materials that the drug product is not equivalent to or substitutable for Premarin is denied. Therefore, for the reasons discussed above, your petition is denied.

Sincerely yours,



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