MEMORANDUM

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

DATE: March 22, 1999

FROM: Director, Center for Drug Evaluation and Research

SUBJECT: Application of 21 CFR 300.50 to Cenestin

TO: Files

I. Introduction

On March 30, 1998, Duramed Pharmaceuticals submitted a new drug application (NDA) for Cenestin, a synthetic estrogen product proposed to be marketed for menopausal symptoms. The issue of applicability of 21 CFR 300.50 has arisen, since the Duramed product is a fixed combination of synthetic conjugated estrogens. For the reasons described below, CDER has concluded that Cenestin falls under section 300.50(c), which states,

> A fixed-combination prescription drug for humans that has been determined to be effective for labeled indications by the Food and Drug Administration, based on evaluation of the NAS-NRC report on the combination, is considered to be in compliance with the requirements of this section.

II. The DESI Findings

Fixed combinations of conjugated estrogens were determined to be effective for menopausal symptoms under the DESI process. On July 31, 1972, FDA published a DESI Notice on Certain Estrogen-Containing Drugs for Oral or Parenteral Use. This notice was based on FDA's evaluation of the Report of the Panel on Drugs Used in Disturbances of the Reproductive System. In this notice (37 FR 14826), FDA stated that certain short-acting estrogens, including certain preparations containing conjugated estrogens, specifically Premarin tablets and Premarin, Intravenous, were effective for the treatment of menopausal syndrome. Subsequently, in a Federal Register notice dated September 29, 1976 (41 FR 43114), FDA reworded this indication as "moderate to severe vasomotor symptoms associated with the menopause." In another notice at the same time (41 FR 43108 (September 29,

1976)), FDA instituted so-called "class labeling" for estrogen products, e.g., uniform labeling on aspects of benefits and risks. Thus, FDA found short-acting estrogen products, including conjugated estrogens, to be effective as a class for the treatment of vasomotor symptoms of the menopause. This finding applies to Premarin notwithstanding the fact that all of the individual active ingredients in Premarin had not been identified and characterized at that time, and still are not today.

III. Extrapolation of DESI Findings to Other Products

FDA regulations state that a DESI notice applies to all drug products that are identical to, related to, or similar to those products specifically listed in that DESI notice (21 CFR 310.6(a)). In the 1970s and 1980s several combination conjugated estrogens products were accepted by FDA and marketed under ANDAs based on a determination that they were similar or related to the conjugated estrogens found effective in the July 31, 1972, DESI notice. These products, often synthesized from plant source material, consist of conjugated estrogens but were termed "esterified estrogens" because they had different proportions of the major conjugated estrogens ingredients than the proportions found in Premarin. However, CDER was able to apply the effectiveness findings in the DESI notice to these products that are similar but not identical to Premarin because of the nature of the indication and the experience at the time with short-acting estrogens for this indication.

The finding of effectiveness of Premarin for menopausal syndrome (not including "dysfunctional uterine bleeding") was based on review of a published uncontrolled clinical case series of the use of Premarin in 61 postmenopausal women, combined with a number of general reviews of the use of estrogens in the treatment of menopause and related conditions, as cited in the report on Premarin Tablets of the Panel on Drugs Used in Disturbances of the Reproductive System. (Goldberg, M.B. "Hormonal and Hormone-like Agents for the Treatment of the Menopause," Medical Management of the Menopause. Grune and Stratton, New York and London, 1959, pp. 48-63; Neustaedter, T. "The Value of Mixed Conjugated Estrogens from Pregnant Mare's Urine in the Treatment of Menopause: A Preliminary Report," *Am. J. of Obstet. Gyn.* 46:530-533, 1943). The basic finding was that short-acting estrogens are effective as replacement therapy for menopausal symptoms brought on by decreased physiologic levels of estrogen: i.e., that estrogen replacement treats estrogen deficiency. Thus, combinations of conjugated estrogens as well as single estrogen products were found effective for menopausal symptoms. The generalizability of the findings across different

types of estrogens is illustrated by the subsequent publication in 41 FR 43108 (September 29, 1976) of the general or "class" labeling previously mentioned. This regulation described for the various types of estrogens the benefits and risks of estrogen use for, among other things, estrogen replacement therapy. This description, as updated in agency guidance, is required to appear in the labeling of all estrogen products.

IV. Applicability of the DESI Findings to Cenestin

The applicability of DESI notices to identical, related, and similar drug products is discussed in 21 CFR 310.6. The main purpose of this rule was to delineate the applicability of DESI findings to marketed products that were not specifically submitted for review to the National Academy of Sciences-National Research Council Drug Efficacy Study Group, but that were nevertheless identical, related, or similar enough to these reviewed products that the DESI findings applied to them as well, thus affecting their status as "new drugs." There is no question of Cenestin's "new drug" status, and an NDA has been filed for it; rather, the issue is whether, for purposes of 300.50, the DESI finding of effectiveness for combinations containing conjugated estrogens can be applied to the combination of estrogens found in Cenestin.

One factor in applying DESI findings to a product not specifically listed in the DESI notice is the similarity of the product to a DESI product. FDA's regulations state at section 310.6(b)(1) that "[a]n identical, related, or similar drug includes . . . any drug moiety related in chemical structure or known pharmacological properties." The preamble to the final rule (37 FR 23185 (October 31, 1972)) discussed applicability in the context of whether qualified experts would conclude that the drug "is sufficiently similar to the drug subject to the [DESI] notices to justify a reasonable application of the efficacy conclusions." In the preamble to a later revision of section 310.6, the agency stated that the final scientific determination that a DESI notice applies to a related product rests with FDA (48 FR 2754 (January 21, 1983)).

Like esterified estrogens, Cenestin is similar or related to Premarin. All the estrogens present in Cenestin are present in Premarin at the same levels. The chemical structure of the Cenestin estrogens is identical to the structure of the major estrogens in Premarin (although Premarin does have additional estrogenic components not present in Cenestin). Because they are all sulfated estrogens, the pharmacological properties of the components of Cenestin are all either identical or similar to the pharmacological properties of the short-acting estrogens in the

1972 DESI notice, which included Premarin. Most of Premarin's estrogenic potency for menopausal symptoms can be attributed to the effects of estrone and equilin, two of the components in Cenestin. (Woodcock memo, May 5, 1997, p. 8).

In fact, the two principal references on which the DESI panel relied in making its finding of effectiveness for conjugated estrogens, including Premarin, focused mainly on estrone and equilin. In one study cited previously, Neustaedter noted that "the predominating component [of Premarin] is estrone sulfate, although presumably smaller amounts of equilin and other estrogens in mare's urine are also present." The other document cited by the panel, "Hormonal and Hormone-like Agents for the Treatment of the Menopause," cited in full previously, listed Premarin as a "modified natural estrogen" with the generic name "sodium estrone sulfate," reflecting the belief at the time that estrone was the major component of the mixture. The mixture of estrogens in Cenestin is clearly similar to the mixture of conjugated estrogens in Premarin, and Cenestin contains the two main components of Premarin, in the same amounts as in Premarin, that the DESI panel considered in making its finding of effectiveness for conjugated estrogens. Given the generalized nature of the indication under consideration in the current situation (menopausal symptoms), the fact that qualified experts at FDA have found that the DESI findings are applicable to other short-acting conjugated estrogens (i.e., to esterified estrogens), and the similarities described above between Cenestin and the short-acting estrogens specifically addressed in the DESI notices, FDA has concluded that, for the purposes of 21 CFR 300.50, the DESI findings for short-acting estrogens, particularly conjugated estrogens, are applicable to the combination of conjugated estrogens found in Cenestin.

Although in May 1997, the Center for Drug Evaluation and Research at FDA found that the Cenestin product could not be considered a generic copy of Premarin because it was not shown to contain all the active ingredients in Premarin (Woodcock memo, May 5, 1997), this conclusion did not reflect doubt that the combination of estrogens in Cenestin would be effective for treatment of menopausal symptoms. Rather, since Cenestin was not proven to be identical to Premarin, proper dosing and effectiveness at various doses had to be demonstrated for Cenestin. These studies on Cenestin have now been completed and accepted by FDA.

V. Conclusion

Under 21 CFR 300.50(c), fixed-combination prescription drugs for humans that have been determined to be effective for labeled indications by the Food and Drug Administration, based on evaluation of the NAS-NRC report on the combination, are considered to be in compliance with the requirements of 300.50. For the reasons described above, the DESI findings for short-acting estrogens, particularly conjugated estrogens, are applicable to the combination of conjugated estrogens found in Cenestin for the purposes of 21 CFR 300.50(c). Therefore, Cenestin is considered to be in compliance with the requirements of the fixed-combination drug policy in 21 CFR 300.50.