

The five applications listed below were approved on the basis of the 1976 notice, and their approvals are withdrawn in a notice published elsewhere in today's issue of the **Federal Register**:

1. NDA 17-968 and ANDA 85-603 (testosterone cypionate 50 milligrams/milliliter (mg/mL) and estradiol cypionate 2 mg/mL injection).
2. ANDA 85-860 and ANDA 86-423 (testosterone enanthate 180 mg/mL and estradiol valerate 8 mg/mL injection).
3. ANDA 85-865 (testosterone enanthate 90 mg/mL and estradiol valerate 4 mg/mL injection).

In 1981, the Center for Drug Evaluation and Research (CDER) (then the Bureau of Drugs) determined in response to requests from the sponsors that the effectiveness finding of the 1976 DESI 7661 **Federal Register** notice could be applied to two combination drug products that were not listed in the 1976 notice, but were being marketed at the time: (1) Conjugated estrogens and methyltestosterone and (2) esterified estrogens and methyltestosterone. Based on this finding, FDA filed (i.e., accepted for review) abbreviated new drug applications (ANDAs) for these drug products. Wyeth-Ayerst submitted ANDA 85-515 for a drug product containing 0.625 mg conjugated estrogens and 5 mg methyltestosterone, and ANDA 87-824 for a drug product containing 1.25 mg conjugated estrogens and 10 mg methyltestosterone. Reid-Provident Laboratories (subsequently acquired by Solvay Pharmaceuticals, Inc.) submitted ANDA 87-212 for a drug product containing 0.625 mg esterified estrogens and 1.25 mg methyltestosterone (Estratest H.S.), and ANDA 87-597 for a drug product containing 1.25 mg esterified estrogens and 2.5 mg methyltestosterone (Estratest).

In 1996, FDA withdrew Wyeth-Ayerst's two pending applications under 21 CFR 314.65 because the applications had been inactive for many years and Wyeth-Ayerst had stopped marketing the products. Solvay continues to market Estratest and Estratest H.S. The ANDAs for the Estratest products have not been approved and are still pending.

FDA has withdrawn approval of all five new drug applications (NDAs) named in the 1972 and 1976 notices. The agency withdrew approval of NDA 10-597 (Tace with Androgen Capsules containing chlorotrianisene and methyltestosterone) and NDA 11-267 (Halodrin Tablets containing fluoxymesterone and ethinyl estradiol) in **Federal Register** notices of June 25, 1993 (58 FR 34466), and March 2, 1994

(59 FR 9989), respectively. The agency withdrew approval of NDA 7-661 (Tylosterone Tablets) and NDA 8-099 (Tylosterone Injection), both containing diethylstilbestrol and methyltestosterone, and NDA 9-545 (Deladumone OB Injection and Deladumone Injection, each containing testosterone enanthate and estradiol valerate) in a notice published in the **Federal Register** of October 29, 1998 (63 FR 58053).

In response to the notice of October 29, 1998, on November 24, 1998, Solvay Pharmaceuticals submitted a citizen petition (Docket No. 98P-1041) requesting that FDA determine that the products covered by the three applications withdrawn in the October 21, 1998, notice were not withdrawn for reasons of safety or effectiveness. As FDA is doing for the five estrogen-androgen combination products whose approvals are being withdrawn in a notice published elsewhere in today's issue of the **Federal Register**, the agency is deferring to the outcome of this proceeding to amend the 1976 notice the determination of whether the products covered by the three applications named in Solvay's petition were withdrawn for reasons of safety or effectiveness. If the proceeding to amend the 1976 notice determines that there is substantial evidence of effectiveness of the estrogen-androgen combination products for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone, then the products covered by the three applications named in Solvay's petition, as well as the five products referred to in a notice published elsewhere in today's issue of the **Federal Register**, will be regarded as not withdrawn for reasons of effectiveness.

As mentioned previously, there are two pending ANDAs for Solvay's Estratest and Estratest H.S., originally filed in 1981. However, as described in detail below, FDA no longer believes that estrogen-androgen combination drug products are effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. FDA, therefore, has initiated this proceeding to amend the DESI finding of effectiveness for these products. This proceeding is limited to a determination of whether there is substantial evidence of the effectiveness of estrogen-androgen combination drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not

improved by estrogen alone. The use of these combination drug products for any other use, including but not limited to the treatment of other menopausal symptoms, will not be considered in this proceeding. The effectiveness of estrogen-androgen combination products for indications not covered by this proceeding should be addressed through the new drug application process.

II. The Safety and Effectiveness of Estrogen-Androgen Combination Drug Products for the Treatment of Vasomotor Symptoms Associated With Menopause in Patients Not Improved by Estrogen Alone

The agency took a renewed interest in estrogen-androgen combination drug products when concerns were raised about the effect of androgens in lowering high-density lipoproteins (Refs.

1 and 2). It is believed that oral androgens can reverse the favorable impact of estrogen on lipoproteins (Ref. 3). Other safety concerns were virilization (Refs. 4 and 5) and possible liver toxicity (Refs. 6, 7, and 8).

FDA concluded that the negative effects androgens may have on lipid profile may be offset by a potential positive effect on bone mineral density (Refs. 1, 9, and 10).

With respect to virilization (i.e., hirsutism, acne, deepening of the voice, alopecia, and clitoromegaly), FDA observed that the incidence varied widely in clinical studies and appeared to be dose and duration dependent. In a 2-year trial of 33 women treated with methyltestosterone 2.5 mg and esterified estrogen 1.25 mg daily, 36 percent reported a hair disorder and 30 percent reported acne (Ref. 1). In the same 2-year trial of 33 women treated with esterified estrogen 1.25 mg daily, 3 percent reported a hair disorder and 6 percent reported acne (Ref. 1). In another trial at 24 months, 10 of the 154 women treated with methyltestosterone and esterified estrogens and 3 of the 157 women treated with esterified estrogens reported hirsutism (Ref. 9).

FDA does not believe there is a serious risk for possible liver toxicity at the relatively low doses of androgen administered in standard oral estrogen-androgen combination therapies (Refs. 11, 12, and 13).

An agency review of the literature regarding safety concerns led to scrutiny of the labeled indication, that is, moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.