June 13, 2003

VIA FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket Number 76N-0377: Studies, Analysis, and Other Information Supporting Request for Hearing

Dear Sir or Madam:

Pursuant to 21 C.F.R. 314.200(c)(2), Syntho Pharmaceutical, Inc., (Syntho) submits studies, analysis, and information in support of its request for a hearing (with three copies of same) in the above-referenced matter.

FDA published in the Federal Register of April 14, 2003, a notice providing an opportunity for a hearing on whether there is substantial evidence of effectiveness of esterified estrogens and methyltestosterone as a combination therapy for moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone and on other related issues. 68 Fed. Reg. 17953 (2003). On May 14, 2003, Syntho filed a notice of participation and request for hearing.

Syntho is an interested party because it manufactures the products Syntest® D.S. and Syntest® H.S. (hereinafter referred to collectively as "Syntest"), which are labeled for use in treating moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.

Syntho offers data, analysis, and other information described below in support of a hearing on the following questions:

(1) Whether there is substantial evidence of effectiveness of esterified estrogens and methyltestosterone for moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone; and

(2) Whether Syntest is a new drug within the meaning of 21 U.S.C. 321(p).

Issues Requiring a Hearing

A. Substantial Evidence of Effectiveness

Products containing esterified estrogens and methyltestosterone, such as Syntest, are labeled for use in treating moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. There are adequate and well controlled studies upon which experts could reasonably rely to recognize these products as effective for this indication.

FDA has proposed to reclassify estrogen-androgen (E-A) drugs as lacking substantial evidence of effectiveness for this indication because the agency has concluded that the combination is no more effective than estrogen alone. 68 Fed. Reg. at 17954. Syntho disagrees with this conclusion for two reasons. First, the conclusion was not based on a consideration of all of the relevant clinical data demonstrating efficacy of the combination for treatment of vasomotor symptoms. Second, the conclusion was based on studies that were not appropriately designed and otherwise failed to support the conclusion.

1. FDA Failed to Consider All Relevant Data Demonstrating Effectiveness.

Four clinical trials (including two trials that were not cited in the FDA analysis appearing in Federal Register notice) provide reliable data demonstrating the effectiveness of the estrogen-androgen combination product in the population of menopausal women whose vasomotor symptoms are not relieved by estrogen alone (Dobs et al. 2002; Greenblatt et al. 1950; Sherwin and Gelfand 1985; Simon et al. 1999). Two of the studies (Sherwin and Gelfand 1985; Simon et al. 1999) were adequate and well controlled studies. All of these studies demonstrated a *greater reduction in vasomotor symptoms from the estrogen-androgen combination in patients with inadequate relief with estrogen alone.*

Simon et al. (1999) conducted a 12-week, double-blind, randomized, placebo-controlled clinical trial to determine the effect of estrogen with and without testosterone, with a placebo controlled group. This study included a low-dose estrogen treatment group (0.625 mg/day esterified estrogen; Estratab®, Solvay Pharmaceuticals, Inc.); a high-dose estrogen group (1.25 mg/day esterified estrogen); low dose estrogen with low dose testosterone (0.625 mg/day esterified estrogen and 1.25 mg/day methyltestosterone; Estratest® HS, Solvay Pharmaceuticals, Inc.); high dose testosterone (1.25 mg/day esterified estrogen and 2.5 mg/day methyltestosterone; Estratest®, Solvay Pharmaceuticals, Inc.); and placebo controls. Results of this study indicate that subjects with low dose estrogen-androgen had fewer somatic symptoms (hot flushes, night sweats, and vaginal dryness) than subjects on low dose estrogen-alone at the 4-week time point. This reduction in symptoms was observed in high-dose estrogen and in the high-dose E-A group as well.

The 1985 study by Sherwin and Gelfand is a prospective, double-blind, placebo-controlled crossover clinical trial in subjects with surgical menopause.

Hysterectomy/oophorectomy subjects were randomized to the two phases of treatment after surgery, each lasting for 3 months. Treatment groups consisted of i.m. injections, and included estrogen with testosterone (7.5 mg estradiol dienanthate, 1.0 mg estradiol benzoate, 150 mg testosterone enanthate); estrogen alone (10 mg estradiol valerate); testosterone alone (200 mg testosterone enanthate), placebo, and hysterectomy control. Somatic score results (hot flushes, sweats, weight gain, rheumatic pains, cold hands and feet, breast pains, headaches, numbness and tingling, skin crawls) improved in the combination estrogen-androgen and androgen groups to a greater extent than in the estrogen-alone and placebo groups ($p<0.01$).

Dobs et al. (2002) conducted a 16-week, double-blind, randomized, parallel group clinical trial in 37 women who were either surgically or naturally menopausal. Subjects were randomly assigned to receive 1.25 mg/d esterified estrogen (Estratab®), alone or with 2.5 mg/day methyltestosterone (Estratest®). Subjects were assessed for a variety of outcomes, including vasomotor problems, every 4 weeks for the duration of the study. Results of this study demonstrated that the combination E-A group showed significant improvements in vasomotor symptoms from baseline, while the estrogen-alone group did not demonstrate statistically significant improvements in this measure.

Greenblatt et al. (1950) conducted a double-blind, placebo-controlled parallel group study to determine the effect of estrogen alone (0.25 mg diethylstilbesterol), estrogen with testosterone (0.25 mg diethylstilbesterol with 5 mg methyltestosterone), testosterone alone, or placebo. In the April 14 Federal Register notice, FDA characterized the results of this study as not supporting the benefit of E-A co-administration. 68 Fed. Reg. at 17955. Although this is an older study, data from this study actually suggest that the combined E-A therapy is superior to estrogen-alone therapy for the treatment of hot flushes and other menopausal symptoms: 89.6% of subjects on the E-A combination treatment reported *complete relief* of hot flushes and associated menopausal symptoms, while 96.5% of subjects on estrogen alone reported only *satisfactory relief* from these symptoms. Complete relief is superior to satisfactory relief. Thus E-A combination therapy showed greater efficacy than estrogen therapy alone.

2. The Studies Cited by FDA Do Not Support Its Conclusion.

In the April 14 Federal Register notice, the agency argues that certain clinical studies support the conclusion that E-A combination therapy is not effective for relief of vasomotor symptoms in patients not improved by estrogen alone. 68 Fed. Reg. at 17955. The studies, however, do not support this conclusion because they were not designed to detect an incremental improvement in vasomotor symptoms. To detect an incremental improvement, the studies should have included the following:

(1) Women who at baseline were inadequately relieved when treated with estrogen alone;
(2) Women with symptoms of a sufficient magnitude so that different levels of relief could be detected;
(3) Women who, once treated with estrogen, would not show the maximum level of relief;

(4) A sufficient sample size to detect an effect.

Eight of the nine studies cited by FDA failed to meet these criteria (*see* Table 1, below), and the ninth study was not adequately powered to support the agency's conclusion. In eight of the nine efficacy studies cited by FDA, the patients were either estrogen responsive (i.e., they had complete relief of their vasomotor symptoms with administration of estrogen alone) or they did not suffer from symptoms of a great enough magnitude to be able to demonstrate an added benefit (Barlow et al. 1986; Barrett-Connor et al. 1999; Hickok et al. 1993; Kaunitz 1997; McNagny 1999; Myers et al. 1990; Sarrel et al. 1998; Watts et al. 1995). Only one of the nine studies was conducted in a patient population that was not responsive to estrogen therapy (Burger et al. 1984). This study showed that the majority of previously unresponsive subjects received added benefit of adding androgens. The study had such a low number of patients, however, that statistical significance could not be shown. These nine studies cannot be relied upon to support a conclusion that E-A combination therapy is not effective for the treatment of vasomotor symptoms.

Table 1

STUDY AUTHORS FED. REG. CITATION NO.	STUDY DESIGN FLAWS
Hickok et al. 1993* Fed. Reg. Reference (FR Ref.) 2	Patients included in the study had very low symptom scores (average score was lower than mild) and included a broad range of symptoms in the composite symptom score in addition to vasomotor symptoms.[1] Also, the authors acknowledge that the study population may have been too small to see a difference between groups.
Barrett-Connor et al. 1999* FR Ref. 9	The authors acknowledge that the study was not designed to detect differences in vasomotor symptom severity. The investigators note that women enrolled did not express dissatisfaction with prior estrogen-alone therapy, indicating that vasomotor symptoms were controlled with estrogen alone. The study design could not detect further improvement since vasomotor symptoms were maximally controlled with estrogen alone. Menopausal symptoms were a secondary endpoint (the authors consider it to be too minor to even show the data).
Watts et al. 1995* FR Ref. 1	The study did not select for women with moderate-to-severe symptoms (the cut-off for inclusion was very mild symptoms – 1 on a scale of 0 to 7 where 7 was severe). By comparing pretreatment mean scores with the average change from baseline it appears that with estrogen alone there was a virtually complete elimination of vasomotor symptoms. It was not possible to detect further improvement with this design.
Sarrel et al. 1998* FR Ref. 17	The authors note that vasomotor symptoms were well controlled with estrogen alone prior to entry into the trial. This design was inadequate to detect differences.

(Table 1 continued on next page)

[1] These included hot flushes, cold sweats, cold hands and feet but also vaginal dryness, breast pain, numbness and tingling, edema, increased facial or body hair, deepening voice, acne, trouble sleeping, heart pounding, dizzy spells, and pressure or tightness in the head or body.

Burger et al. 1984* FR Ref. 18	This study did show a decrease in hot flushes and night sweats in those patients with these symptoms when on estrogen alone (prior to beginning this study). Because the numbers were so low, however, (7 with hot flushes decreased to 3; 6 with night sweat decreased to 2), no statistical difference from pretreatment could be shown. It should also be noted that: the study measured only a complete loss of symptoms; it was not designed to detect decreases in symptom severity.
Myers et al. 1990* FR Ref. 19	Estrogen alone completely relieved symptoms in the study population so no added benefit could be shown. The April 14 Federal Register notice incorrectly cites this study for the proposition that the E-A combination is not effective.[2]
Kaunitz 1997** FR Ref. 3	This is a review citing other studies (Hickok et al. 1993, Myers et al. 1990, Raisz et al. 1996, Watts et al. 1995) that were flawed as discussed in this table.
McNagny 1999** FR Ref. 21	This is a review citing a study (Kaunitz 1997) that was flawed as discussed above.
Barlow et al. 1986* FR Ref. 22	This study does not address the desired population – patients responsive to estrogen
Rymer and Morris 2001** FR Ref. 23	This is a drug information page regarding drugs for treatment of menopausal symptoms. The authors cite Simon et al. 1999, which actually supports the combination E-A therapy for treatment of vasomotor symptoms.
* Study design elements preclude demonstration of an effect. ** Not a clinical study.	

The April 14 Federal Register notice also erroneously cites one review discussion (drug information page) for the proposition that the E-A combination is not effective (Rymer and Morris 2001). The authors actually drew the opposite conclusion, citing the study by Simon et al. that demonstrated the effectiveness of the combination.

3. The Relevant and Appropriately Designed Studies Demonstrate Effectiveness.

Four studies, including two adequate and well controlled studies, support the proposition that E-A combination therapy provides added relief for vasomotor symptoms when estrogen therapy alone is insufficient (Dobs et al. (2002), Greenblatt et al. (1950), Sherwin and Gelfand (1985), and Simon et al. (1999)). All four studies demonstrate that the E-A combination provides a statistically significant further reduction in vasomotor symptoms compared to estrogen alone. Two of the studies are recent, and utilize a relevant formulation and dosage of esterified estrogen and methyltestosterone (Estratest® and Estratest® HD).

There is no study demonstrating that the E-A combination is ineffective. Although the April 14 Federal Register notice cites nine clinical studies in support of the proposition that the E-A combination is not effective for the treatment of vasomotor symptoms, none of these studies supports actually supports the proposition. Eight of the

[2] Even if the design of this study were not flawed, the agency would be required to reassess the study. The April 14 Federal Register notice reports that the estrogen groups had significantly fewer hot flashes than the estrogen-androgen group, whereas the authors report that the steroid groups did not differ significantly from each other at any time point.

nine studies were not designed in such a way as to be able to demonstrate an incremental difference with added androgen and the ninth study showed a numerical advantage for the combination but had too few patients to achieve statistical significance.

B. New Drug Status of Syntest

FDA approval is required only for "new drugs," as that term is defined in 21 U.S.C. 321(p). That section requires a determination that the drug is not generally recognized by qualified experts as safe and effective for its labeled indications.[3]

FDA has addressed the safety of Syntest and of other E-A combination products. Specifically, concerns were raised regarding the lowering of favorable high density lipoproteins (HDLs) with the addition of androgens, the potential for virilization, and the potential for liver toxicity with administration of the combination. The Agency concluded that: (1) "the negative effects androgens may have on lipid profile may be offset by a potential positive effect on bone mineral density," (2) that virilization is dose dependent, and (3) that there is no serious risk for possible liver toxicity at the low androgen doses prescribed in combination products. 68 Fed. Reg. at 17954.

This conclusion is broadly supported in the scientific literature. The weight of the evidence from eight reviews of the clinical use of the E-A combination published since 1995 supports the conclusion that the E-A combination, when administered in the doses recommended in the label, modestly reduces serum HDL levels but poses extremely low concern for virilization and no concern for liver toxicity. The reviews agree, however, that any reversal of estrogen benefit on HDL levels is indeed offset by a positive effect in triglycerides (which are decreased) and bone density (which is increased).

Simon (2001) reviewed the potential for side effects with the clinical use of 1.25 mg esterified estrogen and 2.5 mg methyltestosterone, or the half-dose combination, 0.625 mg esterified estrogen plus 1.25 mg methyltestosterone, in surgically menopausal women. The incidence of adverse lipid effects, liver dysfunction, and virilization were investigated. This author concluded that plasma lipid effects were generally beneficial. Although HDL levels are reduced when E-A therapy is used, triglyceride levels are "markedly" reduced as well. In several 2-year studies and in a meta-analysis of multicenter clinical trials, no liver dysfunction was observed after treatment with labeled doses of the E-A combination product. Virilization with androgen administration is a dose-dependent phenomenon; doses greater than 10 mg/day for 6 months are reported to produce masculinization. At the doses prescribed for E-A combinations, virilization is not a concern. Other benefits include the possible decrease in breast cancer with the combination compared to estrogen alone, positive effects on bone, and vasomotor stability with the combination treatment.

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[3] Although section 201(p) also provides that a drug may be deemed a new drug if it has not been marketed to a material extent and for a material time, this is not an issue. Syntest is a formulary drug that is well accepted in the medical community.

A current review of the benefits of androgens in menopausal women discusses the potential for adverse side effects (Burd and Bachmann 2001). Cosmetic side effects including acne, hirsutism (body and facial hair), and deepening of the voice are stated to occur in some cases of androgen administration.

A thorough review of published literature was published in 1998 (Barrett-Connor 1998). This review cited clear benefits of E-A therapy on bone including inhibition of bone resorption, improved calcium absorption, reduced calcium excretion, and stimulation of bone formation. The effect in bone with E-A is enhanced compared to estrogen alone. Plasma lipoprotein effects from E-A versus estrogen alone include beneficial decreases in low-density lipoprotein cholesterol (LDL), and in triglycerides. HDL cholesterol, however, is also decreased, as reflected by a decrease in apolipoprotein A-I. It is not known whether or not the overall effect is cardioprotective. This review states that adverse effects on liver and blood coagulation parameters are not relevant at doses used in E-A combination products. The only side effect, reported to be reversible and mild, included mild hirsutism, acne, and voice changes in <5% of subjects. The authors conclude that, in subjects with surgical menopause, treatment with E-A products should be considered for its benefits.

The addition of androgens to menopausal hormone replacement therapy was reviewed by Kaunitz (1997) and Gelfand and Wiita (1997). Risks and side effects of the addition of androgens to estrogen therapy included lipoprotein effects (diminution of the beneficial increase in HDLs generally seen with estrogen alone), and virilizing effects (hirsutism and acne in some but not all studies). Liver effects were reported not to occur at doses in E-A combination therapy. The benefits of E-A therapy on bone density were also described.

A review of Solvay Pharmaceuticals, Inc.'s post-marketing safety surveillance data was published (Phillips and Bauman 1997). This safety profile was based on 568 spontaneously reported cases, comprising 863 adverse events (AEs); two-thirds of the AEs were from patients on Estratest® and one-third from patients on the half-strength formulation. The conclusion of the post-marketing surveillance report was that Estratest® and Estratest® HS do not pose a safety concern. No deaths, reports of cancer, cardiovascular disease, thromboembolisms, or hepatic dysfunction occurred that were related to treatment. The authors report that 23/568 cases (4.0%) had at least 1 serious event and 53/863 adverse events (6.1%) were serious. Of the cases determined to be serious, the majority were considered unrelated or of unknown relation to treatment (they were related to preexisting conditions or an unrelated condition). Hepatic effects in 4 cases had limited information and were not consistent with changes observed with high-dose androgens. The only adverse event that was reported to be related to A-E administration was virilization; 220/863 of all adverse events (25.5%) were classified as a virilizing symptom. Interestingly, there was equal distribution of symptoms in the Estratest® and half-strength Estratest® HS groups. Alopecia (12% of patients), acne (4.9% of patients), hirsutism (4.7% of patients), and seborrhea (1% of patients) were the virilizing symptoms most frequently reported.

E-A hormone replacement therapy is discussed in a review by Rosenberg et al. (1997). Benefits of this combination treatment are discussed (increased bone mineral density, increased sexual functioning, and psychological benefits), as well as potential adverse effects. The potential for virilization is low because of low doses used. Hepatic toxicity has been shown not to develop in women administered doses of E-A as per current labeling recommendations.

In a review of exogenous androgens in postmenopausal women, the occurrence of adverse events is discussed (Sands and Studd 1995). Equivocal effects of the E-A combination on plasma lipids is presented. Some reports show a prevention of estrogen-mediated HDL increases (not a benefit) and some report enhanced reduction of LDL cholesterol (a benefit), while others report no change. At that time it was concluded that further study of this phenomenon is warranted.

In sum, eight recent reviews of the literature on the clinical safety of E-A combination therapy generally agree that liver toxicity and virilization effects are dependent on dose, and are not of concern at the low doses prescribed. Further, if virilization effects were to occur, they could be reversed by cessation of treatment. Finally, concerns about lipoprotein effects of the E-A combination may be unwarranted, as both positive and negative changes in plasma lipids are observed. Further, other benefits of E-A combination products on bone density should be considered. E-A therapy is not a safety concern in patients when used according to the directions in the product label. This literature reflects general agreement among qualified experts that Syntho's combination of esterified estrogens and methyltestosterone is safe for its labeled indication.

As discussed above, the combination of esterified estrogens and methyltestosterone has been demonstrated effective based on adequate and well controlled studies published in the scientific literature. The experts addressing these issues in the published literature recognize that the combination of esterified estrogens and methyltestosterone found in Syntest to be effective for moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.

For all of the foregoing reasons, Syntho respectfully requests a hearing on the questions of (1) whether there is substantial evidence of effectiveness of esterified estrogens and methyltestosterone products for their labeled indication and (2) whether

Syntest is generally recognized as safe and effective within the meaning of 21 U.S.C. 321(p).

Respectfully submitted,

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