DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Solvay Pharmaceuticals, Inc. Estratest® and Estratest®HS; Proposal to Reclassify Estrogen-Androgen Combination Drugs as Lacking Substantial Evidence of Effectiveness; Opportunity for a Hearing	)	Docket Nos. 76N-0377 and 98P-1041 DESI No. 7661

SUBMISSION OF DATA, INFORMATION, AND ANALYSES IN SUPPORT OF HEARING REQUEST MADE ON BEHALF OF SOLVAY PHARMACEUTICALS, INC.

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The Federal Register published on April 14, 2003, contained a Notice (the "Notice") proposing to reclassify certain estrogen-androgen combination drugs as lacking substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms associated with the menopause in patients not improved by estrogen alone on the basis that there is not substantial evidence of the contribution of each component to the effectiveness of these combination drugs. 68 Fed.Reg. 17953. Solvay Pharmaceuticals, Inc. ("Solvay") is the holder of the pending abbreviated new drug applications ("ANDAs") for Estratest® and Estratest® H.S., both of which are identified in the Notice as subject to the Food and Drug Administration's ("FDA's") proposal.

On May 6, 2003, the undersigned, on behalf of Solvay, submitted a timely request for hearing in accordance with the April 14, 2003 Notice and FDA regulations set forth at 21 C.F.R. § 314.200(c)(1)(i). The submission herein contains the data, information, and analyses relied upon by Solvay to support its request for hearing with respect to Estratest® and Estratest® H.S.

In addition, this submission contains argument and analysis supporting Solvay's contention that FDA's proposed actions cannot be justified factually or legally, and thus that Solvay is entitled as a matter of law to summary judgment in its favor and rescission of the Notice. See 21 C.F.R. § 314.200(g)(4).

In the event that the Notice is not rescinded or summary judgment is not granted in favor of Solvay, the company is nevertheless entitled to a hearing because material issues of fact cannot be disposed of by FDA's summary judgment procedures, but rather must be resolved through the conduct of a hearing.

I. FACTUAL BACKGROUND

A. Under The DESI Program, Estrogen-Androgen Combination Drug Products Were Rated "Effective"

During the Drug Efficacy Study Implementation ("DESI") review, the National Academy of Sciences/ National Research Council ("NAS/NRC") evaluated the effectiveness of a number of estrogen-androgen fixed combination products. In 1970, FDA published an announcement that Halodrin Tablets (fluoxymesterone with ethinyl estradiol) was possibly effective for the treatment of the menopausal syndrome. 35 Fed.Reg. 7464 (May 13, 1970) (DESI 11267). In 1972, FDA reclassified estrogen-androgen combination drugs as effective for the prevention of postpartum breast engorgement and for the menopausal syndrome in those patients not improved by estrogen alone. 37 Fed.Reg. 18225, 18226 (Sept. 8, 1972) (DESI 7661).

Four years later, in 1976, FDA issued another Federal Register notice pertaining to estrogen-androgen combination products, stating that it was rewording the indications deemed to be effective in the 1972 notice "to coincide with the physician labeling for estrogens for general use published elsewhere in this issue of the Federal Register." 41 Fed.Reg. 43112 (Sept. 29, 1976). The indication relevant to this proceeding was reworded to treatment of "moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions)." Id. at 43113. There was no further explanation of the change in indication from "menopausal syndrome" to "vasomotor symptoms." The notice of opportunity for hearing included in the 1976 Federal Register notice applied only to those parties who sought to raise issues relating to the "indication(s) lacking substantial evidence of effectiveness" to which the

notice referred, *i.e.*, post-menopausal and senile osteoporosis, osteoporosis in certain patients following long-term adrenocortical therapy, prevention of postpartum breast manifestations of lactation, protein depletion and chronic debility, tissue atrophy in geriatric patients, depletion of protein and osseous tissues during corticosteroid therapy, spinal paraplegia and delayed fracture union, and dysmenorrhea. Id. at 43112, 43113. It did not provide a notice of opportunity for hearing for parties raising issues relating to the rewording of the effective indications.

The approvals of all five new drug applications ("NDAs") named in the 1972 and 1976 DESI notices have been withdrawn. The notice of withdrawal of approvals of NDA 10-597 (Tace with Androgen Capsules containing chlorotrianisene and methyltestosterone) and NDA 11-267 (Halodrin Tablets containing fluoxymesterone and ethinyl estradiol) were published in the Federal Registers of June 25, 1993 (58 Fed.Reg. 34466), and March 2, 1994 (59 Fed.Reg. 9989), respectively. The notice of withdrawal of 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) was published in the Federal Register of October 29, 1998 (63 Fed.Reg. 58053).

In the Federal Register of December 17, 1998, FDA withdrew approval of estrogen-containing drugs insofar as they are indicated for postpartum breast engorgement on the basis that estrogens have not been shown to be safe for this use. 63 Fed. Reg. 69631 (Dec. 17, 1998).

B. Estrogen-Androgen Combination Products Were On the Market Even Prior To The DESI Review

Well before the initiation of the DESI program, at least one product similar and related to the Estratest® products was established on the market. Ayerst Laboratories began marketing

Premarin (conjugated estrogen) with methyltestosterone ("Premarin MT") in 1950. Prior to 1962, Premarin MT was generally recognized in the medical literature as safe and effective, and was never covered by an effective new drug application. Ayerst therefore took the position that Premarin MT was an "old drug" not subject to the premarket approval requirements applicable to new drugs.

In November 1976, after the DESI review of estrogen-androgen combination products, Ayerst submitted ANDAs for two strengths of Premarin MT. In December 1976, FDA rejected the Premarin MT ANDAs. Ayerst argued in response that the Premarin MT ANDAs were appropriate under the DESI review program. In August 1977, in response to an FDA request, Ayerst submitted to the Agency the Premarin MT labeling. Thereafter, in October 1977, FDA requested patient package insert labeling for Premarin MT to which Ayerst responded in December 1977. In June 1980, despite requesting labeling for Premarin MT under the filed ANDAs, FDA sent Ayerst a regulatory letter taking the position that Premarin MT was an unapproved and misbranded drug and must be removed from the market.

Ayerst responded to this letter, citing the history and mishandling of the Premarin MT applications by the Agency. Ayerst asserted that Premarin MT was therapeutically equivalent to the estrogen-androgen combination products reviewed and found effective under the DESI program. In addition, Ayerst filed a citizen petition demanding that DESI 7661 be amended to include Premarin MT. In the citizen petition, Ayerst threatened a lawsuit citing the inconsistencies in FDA's decisions regarding "grandfathered" compounds following the DESI review. Ayerst continued to market the Premarin MT products until 1996, when Ayerst's

pending applications for Premarin MT were withdrawn under 21 C.F.R. § 314.65 because the company had stopped marketing the products.

C. History Of The Marketing Of The Estratest® Products

Reid-Provident Laboratories, Inc., Solvay's predecessor in name, began to market Estratest® in 1965 and Estratest®HS in 1975. Although the Estratest® products were not specifically identified by the DESI 7661 panel, FDA's policy was that every DESI notice applied both to the drug(s) specifically identified therein and to all identical, related, and similar drug products. 37 Fed.Reg. 2969 (Feb. 10, 1972); 37 Fed.Reg. 23185 (Oct. 31, 1972). Under the DESI program, FDA invited firms marketing or wishing to market drug products identical, similar, or related to products specifically identified as effective by FDA to submit ANDAs for their products.

While specifically noting that the Estratest® products were not new drugs and therefore could be marketed without premarket clearance, Reid-Provident prepared and submitted ANDAs for Estratest® and Estratest®HS to FDA in 1979. Initially, FDA questioned the acceptability of the Estratest® ANDAs under the DESI program procedures. In a February 5, 1981 letter to the Agency, however, Reid-Provident addressed FDA's questions, presenting, among other things, a statement by the relevant DESI panel chairman that the Estratest® formulations were within the class of products ruled safe and effective by the expert panel. In a May 1, 1981 letter to Reid-Provident accepting the receipt of the ANDA for Estratest®HS, the Agency accepted the position set forth by the company in its February 5, 1981 letter.

In September 1981, the Office of Generic Drugs requested a bioavailability study for the methyltestosterone in the Estratest® products. In January 1982, Reid-Provident requested a

waiver of this bioavailability study requirement because methyltestosterone concentrations in serum would be undetectable using even the most sophisticated methods available at that time. In April 1982, FDA responded that the Agency cannot grant waivers of bioavailability requirements on the basis of lack of sufficiently sensitive methodology and indicated that Reid-Provident was responsible for developing the required assays. In January 1983, Reid-Provident informed FDA that it had contacted several laboratories and that no methods were available to measure such low amounts in serum and that although a radioimmunoassay could possibly be developed, there was no assurance that it would work. Reid-Provident therefore again requested a waiver from the requirement for bioavailability studies. On March 17, 1983, the Office of Generic Drugs informed Reid-Provident that a waiver could not be granted.

For the next approximately thirteen years, Reid-Provident/Solvay diligently worked with FDA to develop a methodology to reliably detect low levels of methyltestosterone and thereby generate the data considered by FDA as necessary to support approval of the Estratest® ANDAs. On April 7, 1983, Reid-Provident submitted a bioavailability protocol to the Office of Generic Drugs. On July 8, 1983, FDA responded that the bioavailability protocol was not acceptable. Thereafter, on April 26, 1985, Reid-Provident submitted another protocol to evaluate the bioavailability of methyltestosterone in Estratest® versus an oral solution of methyltestosterone. On August 27, 1985, FDA provided comments on the proposed bioavailability protocol, informing Reid-Provident of various requirements. On November 12, 1990, after years of attempts to locate and/or develop a valid and adequately sensitive method for measuring methyltestosterone at low concentrations in serum, Reid-Provident submitted another bioavailability protocol to FDA.

Between January 29, 1991, and May 20, 1992, FDA made various requests for data relating to dissolution issues. On September 9, 1992, Solvay requested a meeting to discuss the definitive bioavailability study and submitted a pre-meeting packet. During a December 2, 1992 meeting, FDA indicated that it needed more time to review and comment on the pilot bioavailability study and advised Solvay to wait for comments before beginning the study. On March 1, 1994, Solvay submitted to the Office of Generic Drugs the report of the definitive pharmacokinetic and bioavailability study comparing Estratest® and a reference oral solution. On April 12, 1994, Solvay submitted bioanalytical test methods and validation reports to support the bioavailability study.

On July 22, 1994, Solvay submitted a major CMC amendment to the ANDAs. On May 17, 1995, the Office of Generic Drugs responded to the major amendment with CMC and labeling deficiencies. On July 7, 1995, Solvay participated in a teleconference with FDA regarding the Agency's labeling comments. On September 14, 1995, FDA issued a letter to Solvay regarding the bioavailability study to which Solvay responded on March 29, 1996. On February 1, 1996, Solvay responded to the Agency's May 17, 1995 deficiency letter. On June 21, 1996, the Office of Generic Drugs responded to Solvay's February 1, 1996 response indicating further deficiencies.

By mid-1997, however, approval of the Estratest® applications appeared imminent. In a letter dated January 15, 1997, FDA notified Solvay that it had completed review of the bioavailability submission and had no further questions concerning that aspect of the ANDAs. In correspondence to Solvay dated March 3, 1997, the Agency identified as "minor" the remaining deficiencies in the applications. At the same time, a review of final product labeling

was conducted by the Agency. In a letter dated May 15, 1997, the Agency requested Solvay's cooperation in methods validation testing for both Estratest® preparations — a recognized customary step in the process of final approval of a drug product. As requested by the Agency, final printed labeling was hand-delivered on August 1, 1997, a further indication that approval was imminent. Because of placement of Solvay on the Application Integrity Policy ("AIP") list in 1997, however, FDA did not approve the pending Estratest® ANDAs.

On November 6, 1998, FDA sent a letter to Solvay informing the company that its Estratest® ANDAs were not approvable because the listed drugs that served as the basis for the ANDAs were withdrawn "for ... effectiveness under 21 CFR 314.150(a)" in the October 29, 1998 Federal Register and that the continued marketing of these drugs without an approved NDA constituted a violation of Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("Act"). On November 13, 1998, Solvay requested a hearing on the approvability of the Estratest® ANDAs with a specific notation that the request should not be construed as an admission that an NDA/ANDA is required to market the products. Indeed, the November 13, 1998 request for a hearing specifically identified, in accordance with FDA's regulations, that one of the issues to be presented at the hearing was the not "new drug" status of the Estratest® products. On November 24, 1998, Solvay further responded to the Agency's November 6, 1998 letter: (a) disagreeing with FDA's conclusion that "there is not a significant patient population requiring the concurrent therapy of an estrogen and an androgen in a fixed dose;" (b) asserting that a reference listed drug was not required because the concept of "reference listed drug" did not exist at the time of filing the Estratest® ANDAs; and (c) arguing that FDA's decisionmaking was procedurally flawed and denied Solvay fair process.

FDA did not respond to Solvay's November 13, 1998 request for a hearing or its November 24, 1998 letter challenging the factual, legal, and procedural bases underlying the Agency's November 6, 1998 letter until it published the April 14, 2003 Notice and on the same date sent a letter to Solvay explaining its actions. The Agency's April 14, 2003 letter informed Solvay "that it does not intend to rely on the argument that there is no appropriate reference listed drug (RLD) for the ANDAs ... and therefore the Agency is rescinding those portions of the November 6, 1998, letter refusing to approve the two ANDAs on the grounds that there is no appropriate RLD." Based upon this rescission, FDA advised Solvay that its November 13, 1998 request for a hearing was "rendered moot."

Indeed, while continuing to take issue with the approvability of the Estratest® ANDAs, the April 14, 2003 Federal Register Notice specifically acknowledges that the ANDAs are still "pending." 68 Fed.Reg. 17953, 17954. The April 14, 2003 Federal Register Notice also acknowledges that the ultimate approvability of the ANDAs is dependent upon the appropriateness of the Agency's April 14, 2003 Federal Register Notice proposing to amend the DESI "effective" classification to "lacking substantial evidence of effectiveness" based upon the Agency's view that the data analyzed in the Federal Register Notice do not establish the contribution of each of the components to the effectiveness of the products. Id.

Also on November 24, 1998, Solvay responded directly to the notice of October 29, 1998, in the form of a citizen petition (Docket No. 98P-1041) requesting that FDA determine that the products covered by that notice were not withdrawn for reasons of safety or effectiveness. The Agency first addressed this citizen petition in its April 14, 2003 Notice. In that notice, FDA indicated that it is deferring the determination of whether the products covered

by the three applications named in Solvay's petition were withdrawn for reasons of safety or effectiveness pending the outcome of the current proceeding to amend the 1976 notice. Id.

II. SAFETY HAS NOT BEEN PLACED AT ISSUE BY THE PROPOSED ORDER

FDA's proposed order to reclassify certain estrogen-androgen combination drugs as lacking substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms associated with the menopause in patients not improved by estrogen alone does not allege lack of safety or inadequate proof of safety as a ground for the Agency's proposed action. Rather, the proposed order is based solely on the assertion that "for this indication there is not substantial evidence of the contribution of each component to the effectiveness of these combination drugs." 68 Fed.Reg. at 17953. See also id. at 17955 ("FDA believes that substantial evidence is lacking that the addition of an androgen can improve the effectiveness of estrogen alone in the treatment of vasomotor symptoms (i.e., hot flushes)"). Accordingly, as provided for in 21 C.F.R. § 314.200(d)(3), Solvay does not specifically set forth evidence in this submission to establish the safety of the Estratest® products. Nevertheless, certain points related to safety may be relevant to the compliance of the Estratest® products with the Agency's combination drug policy, and these issues are discussed in the appropriate sections below. Solvay also reserves its right to offer safety evidence in rebuttal, if necessary.

III. EFFECTIVENESS DATA

Section IV.B. below sets forth the basis for the conclusion that each component of the Estratest® products contributes to the products' effectiveness for their labeled indication, including a description of the relevant controlled clinical studies. The Point-by-Point analyses and supporting documentation attached hereto demonstrate that the controlled clinical studies

that establishes the effectiveness of the Estratest® products satisfy the criteria required by 21 C.F.R. § 314.126.

Volumes 4 through 20 are confidential, as they include proprietary studies and analyses conducted by or for Solvay. Volumes 1 through 3 are not confidential. These volumes contain this summary of the data, analyses, and views in support of Solvay's request for a hearing, declarations from respected experts, published articles and other data and information on which Solvay relies.

IV. SUMMARY JUDGMENT MUST BE ENTERED FOR SOLVAY

As set forth more fully below, Solvay is entitled to rescission of the Notice and summary judgment in its favor.

A. FDA Has Failed To Allege A *Prima Facie* Case

FDA's Notice to amend the long-standing DESI classification of estrogen-androgen combination products from "effective" to "lacking substantial evidence of effectiveness" can be supported only if the Agency sets forth new information that would justify the proposed change. See, e.g., Harrington v. Chao, 280 F.3d 50, 58 (1st Cir. 2002) ("An agency's decision cannot simply depart from the agency's prior precedent without explaining its reasons for doing so") (citing Atchison, Topeka & Santa Fe Ry. Co. v. Wichita Bd. of Trade, 412 U.S. 800 (1973)); Gilbert v. NLRB, 56 F.3d 1438, 1445 (D.C. Cir.1995) ("It is, of course, elementary that an agency must conform to its prior decisions or explain the reason for its departure from such precedent"); Office of Com. of United Ch. of Christ v. FCC, 707 F.2d 1413, 1426 (D.C. Cir. 1983) ("if the Commission should alter a policy and yet fail to recognize the change or fail to provide either adequate explanation or adequate consideration of relevant factors and

alternatives, we must set aside the Commission's action and remand for further proceedings"); Baltimore & Annapolis R. Co. v. WMATC, 642 F.2d 1365, 1370 (D.C. Cir. 1980) ("it is vital that an agency justify a departure from its prior determinations").

If the April 14, 2003 Notice is finalized, it would effectively withdraw the opportunity for Solvay to obtain ANDA approval for the Estratest® products. See 57 Fed.Reg. 17950-01, 17963 (April 28, 1992) (An applicant may refer to the Agency's conclusions in the relevant DESI notice about the product's safety and effectiveness to satisfy the full reports of investigations requirement under Section 505(b)(1)(A) of the Act and must demonstrate only that the proposed drug product is bioequivalent to the drug product that is the subject of the relevant DESI notice). This proceeding is therefore analogous to the withdrawal of an NDA/ANDA. Indeed, in the Notice, FDA requires that interested persons with the desire to challenge the proposed reclassification follow the NDA procedures set forth in 21 C.F.R § 314.200. 68 Fed.Reg. 17953, 17957. Accordingly, the Notice must be premised on Sections 505(e)(1) through (3) of the Act, which state:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that the drug is not shown to be safe for use under the conditions of use when the application was approved, or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application

> was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof...

21 U.S.C. § 355(e)(1)-(3).

Thus, under the Act (and the Administrative Procedures Act), if the Agency concludes that the DESI "effective" classification should be changed to "lacking substantial evidence of effectiveness" on the basis that the data do not establish that each of the components contribute to the product's effectiveness, it is required to provide a detailed analysis of the new evidence or information which justifies the change. The D.C. Circuit has repeatedly expressed this view:

> We shall expect the FDA to make its criticisms express and detailed, and to cite precisely to the pertinent regulations and evidentiary flaws. The regulations are extensive and technical; submitted evidence is typically abstruse and voluminous, Courts cannot efficiently shoulder their heavy burden of review under Hynson unless the Administration's orders make utterly transparent why each piece of submitted evidence fails the particular regulatory provisions relied upon.

Cooper Lab., Inc. v. Comm'r, 501 F.2d 772, 787 (D.C. Cir. 1974). See also American Cyanamid Co. v. FDA, 606 F.2d 1307, 1311 n.16 (D.C. Cir. 1979). Only when FDA has satisfied this initial burden must the manufacturer come forward with contrary evidence. USV Pharm. Corp. v. Secretary of HEW, 466 F.2d 455, 461 (D.C. Cir. 1972). Thus, a manufacturer may prevail simply by pointing out the inadequacies in FDA's initial showing. Hess & Clark, Div. of Rhodia, Inc v. FDA, 495 F.2d 975, 992 (D.C. Cir. 1974).

As discussed in detail below, the evidence presented in this submission conclusively establishes that the Estratest® products are both safe and effective. However, even if Solvay had presented no evidence whatsoever, FDA's proposal to classify the Estratest® products as lacking

substantial evidence of effectiveness could not be sustained on the basis of the extremely limited facts alleged in the Notice. As noted, FDA has the burden of proving that "new information" indicates that there is a lack of substantial evidence that each component of the Estratest® products contribute to their effectiveness. 5 U.S.C. § 556(d); 21 U.S.C. § 355(e)(3); Hess & Clark, 495 F.2d at 984, 992.

In the Notice, FDA states: "The agency has closely examined the data and information that formed the basis for the 1976 finding that such combinations were effective for this indication, as well as the subsequent literature, and has determined that there is a lack of substantial evidence that this combination is effective for 'moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.'" 68 Fed.Reg. at 17955. It further states: "The agency is taking this action because for this indication there is not substantial evidence of the contribution of each component to the effectiveness of these combination drugs." Id. at 17953. The Notice nevertheless provides only a cursory analysis of a limited number of the studies relevant to the effectiveness of estrogen-androgen combination products. Such minimal allegations do not satisfy FDA's initial burden of presenting "new information" indicating "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 355(e)(3). See Hess & Clark, 495 F.2d at 992; USV Pharm. Corp., 466 F.2d at 461.

Moreover, in order to amend a DESI "effective" classification, FDA cannot meet its burden merely by asserting that the evidence to support the contribution of each component to the effectiveness of the products does not meet today's interpretation of "substantial evidence."

Most, if not all, products reviewed under the DESI program and found effective by the NAS/NRC and FDA would not satisfy FDA's current interpretation of "substantial evidence." Accordingly, the contribution of each component to the effectiveness of the Estratest® products must be assessed under the standards that were in effect when the products were subject to review and classification. See, e.g., Serono Lab., Inc. v. Shalala, 158 F.3d 1313, 1322-23 (D.C. Cir. 1998). Indeed, FDA acknowledged that this is the appropriate standard in its combination policy: combination products that were found to be effective under the DESI review (such as the Estratest® products) are considered to be in compliance with the combination policy even if they would not meet the Agency's current standards for compliance with the combination policy. 21 C.F.R. § 300.50(c). See Section IV.B.2.c., below.

FDA has presented no new evidence or information that establishes that either of the previous DESI "effective" classifications for estrogen-androgen combination drug products was or is inappropriate. The evidence cited by the Agency is either inconclusive or confirms the appropriateness of the determination that estrogen-androgen combination products are safe and effective and constitute rational therapy for the menopausal syndrome/vasomotor symptoms. Further, FDA's 1980 approval of Upjohn's NDA for Depo-Testadiol (estradiol cypionate and testosterone cypionate) (NDA 17-968) without submission of any clinical data (*i.e.*, only bioavailability data was required) demonstrates that FDA has either recognized the existence of sufficient data supporting the effectiveness of the combination in compliance with 21 C.F.R. § 300.50 or has effectively waived the need for such data for combination estrogen-androgen

products offered for relief of the menopausal syndrome/vasomotor symptoms, including the Estratest® products, pursuant to 21 C.F.R. § 314.126(c).[1]

Moreover, amending the DESI 7661 "effective" classification without presenting new evidence or information affirmatively justifying such an amendment would result in similar situations being treated in a dissimilar manner and would therefore be arbitrary and capricious under the Administrative Procedures Act ("APA"). As noted above, most, if not all, of the products reviewed under the DESI program and found effective by the NAS/NRC and FDA would not satisfy FDA's current interpretation of "substantial evidence." Further, FDA approved Depo-Testadiol in 1980 without requiring submission of clinical data. Courts have consistently held that "[a]n agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so." Independent Petroleum Ass'n of Am. v. Babbitt, 92 F.3d 1248, 1258 (D.C. Cir. 1996) (citations omitted). See also U.S. v. Diapulse Corp. of Am., 748 F.2d 56, 62 (2d Cir. 1984) (FDA must "not 'grant to one person the right to do that which it denies another similarly situated'") (quoting Marco Sales Co. v. FTC, 453 F.2d 1, 7 (2d Cir. 1971)). "If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA." Allergan, Inc. v. Shalala, 6 Food and Drug Rep. 389, 391, No. 94-1223 (D.D.C. Nov. 10, 1994). See also Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 28 (D.D.C. 1997). Accordingly, FDA cannot require the Estratest® products to meet today's standards for proof of effectiveness, unless it likewise requires all other marketed DESI products to meet the same standard.

[1] Earlier this year, Pharmacia & Upjohn Co. requested that FDA withdraw approval of the NDA for Depo-Testadiol on the basis that the product was no longer marketed by the company. 68 Fed.Reg. 17957 (April 14, 2003).

In sum, even if one were to assume the truth of FDA's allegations, they do not provide a valid legal basis under the Act or the APA to justify FDA's proposed action. FDA has not adduced legally viable grounds to support the action proposed in the Notice to change the classification of estrogen-androgen combination products from "effective" to "lacking substantial evidence of effectiveness." Consequently, the Notice must be rescinded and summary judgment granted in favor of Solvay. 21 C.F.R. § 314.200(g)(4).

B. Solvay Has Submitted Data That Conclusively Demonstrate That Each Component Of The Estratest® Products Contributes To The Products' Effectiveness For Their Labeled DESI "Effective" Indications And, Accordingly, Summary Judgment Should Be Entered In Solvay's Favor

The Agency's regulations provide that if the evidence presented by Solvay establishes that the grounds cited in the Notice are not valid, the Commissioner must enter summary judgment for Solvay and rescind the Notice. 21 C.F.R. § 314.200(g)(4). As set forth in detail below, the data submitted herewith, as well as data previously submitted to the Agency, conclusively demonstrate that each component of the Estratest® products contributes to the products' effectiveness for the labeled indication. Accordingly, the grounds stated in FDA's April 14, 2003 Notice are not valid and summary judgment must be entered for Solvay.

1. The Estratest® Products Are Generally Recognized As Safe And Effective And Have Been Marketed For A Material Time And To A Material Extent

The Estratest® products are not "new drugs," as defined in the Act, 21 U.S.C. § 321(p), and are therefore not subject to premarket approval requirements applicable to new drugs (21 U.S.C. § 355). A product is not a "new drug" — and is commonly referred to as an "old drug" — if it is generally recognized among qualified experts as safe and effective for use under the

conditions described in its labeling and has been used to a material extent and for a material time under such conditions (known as "GRASE"). 21 U.S.C. § 321(p).

As explained above, estrogen-androgen fixed dose combination products were rated "effective" for vasomotor symptoms in those patients not improved by estrogen alone by the NAS/NRC as part of the DESI program, and FDA adopted this finding. In adopting the NAS/NRC Panel's recommendations regarding the effectiveness of estrogen-androgen combinations, FDA specifically concluded that estrogen-androgen fixed dose combination products are effective for vasomotor symptoms in those patients whose symptoms are not adequately addressed by estrogen therapy alone.

The NAS/NRC Panel's conclusion that estrogen-androgen combinations are "effective" in treating vasomotor symptoms, which was based primarily on data in the published literature, constitutes the factual and legal justification for treating the Estratest® products as "old drugs" (*i.e.*, generally recognized as safe and effective by qualified experts). Since the Panel reached its conclusion, further reports in the published literature have provided additional evidence in support of the general recognition of the safety and effectiveness of estrogen-androgen combination products in general and the Estratest® products in particular. See Section IV.B.2.d., below. Moreover, the Estratest® preparations have been used to a material extent and for a material time for the treatment of vasomotor symptoms in those patients whose symptoms are not adequately addressed by estrogen therapy alone, in that Solvay and its predecessor Reid-Provident have continuously and extensively marketed the Estratest® products as "old drugs" for this indication since 1965. Further, as noted above, a very similar product, Premarin MT

(conjugated estrogen and methyltestosterone) was marketed as an old drug from 1950 until 1996 and was removed from the market in 1996 solely for commercial reasons.

Even if it is the case that the existing published data relating to the safety and effectiveness of the Estratest® products would not meet the current standard of "at least 'substantial evidence' of effectiveness for approval of an NDA,"[2] in the absence of new data or information to the contrary, the current standard for approval of an NDA should not be applicable to a product which entered the market when a different standard (*i.e.*, definition of substantial evidence) was applied. Rather, established FDA policy and practice indicates that, under such circumstances, the approval criteria in effect at the time of the initial marketing of the Estratest® products should be applied, and the courts have upheld the legality of this policy. See Serono, 158 F.3d at 1322-23.

In other words, the available safety and effectiveness data in existence at the time the Estratest® products entered the market was adequate to support approval of an application (*i.e.*, substantial evidence of effectiveness, as this standard was then interpreted). This is clear from the fact that FDA was willing to approve the combination of estrogen and androgen in a fixed dose without submission of clinical data (*i.e.*, by accepting and reviewing the Estratest® ANDAs) and indeed did approve Upjohn's Depo-Testadiol in 1980 without the submission of clinical safety and effectiveness data. Thus, the standard for general recognition of safety and effectiveness of the Estratest® products ought to be the quantity and quality of data that was required to obtain new drug approval in 1965, which the Estratest® products clearly meet.

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[2] Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609, 629 (1973) (defining the burden of demonstrating GRASE). See also 21 C.F.R. § 314.200(e)(1).

2. FDA's DESI "Effective" Classification of Estrogen-Androgen Combination Products Was, And Continues To Be, Correct

As noted above, in adopting the NAS/NRC Panel's recommendations regarding the effectiveness of estrogen-androgen combinations, FDA specifically concluded that estrogen-androgen fixed dose combination products such as the Estratest® products are effective for the treatment of vasomotor symptoms in those patients whose symptoms are not adequately addressed by estrogen therapy alone. As set forth below, the clinical data establish that the Estratest® products are effective for the treatment of vasomotor and related symptoms of the menopausal syndrome in those patients whose symptoms are not adequately addressed by estrogen therapy alone.

a. "Vasomotor Symptoms" Encompasses A Constellation Of Intertwined Symptoms Of The Menopausal Syndrome

As set forth above, in 1976 FDA reworded the indication for estrogen-androgen combination products deemed to be effective in the 1972 notice from treatment of the "menopausal syndrome in those patients not improved by estrogen alone" to treatment of "moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions)." FDA explained that this "rewording" was done "to coincide with the physician labeling for estrogens for general use published elsewhere in this issue of the Federal Register." 41 Fed.Reg. 43112, 43113 (Sept. 29, 1976). There was no medical or scientific justification cited for this rewording of the indication for estrogen-androgen combination products. Further, as discussed below, it does not appear that the change in language

significantly changed the scope of the indication, thus indicating that FDA did not at that time intend the rewording to materially change the scope of the indication.

In the April 14, 2003 Notice, however, FDA appears to reinterpret the revised DESI-effective indication for estrogen-androgen products as follows:

> [V]asomotor symptoms associated with the menopause are, simply put, 'hot flushes.' A hot flush is a sudden feeling of heat, usually on the face, neck, shoulders, and chest. Hot flushes have been described as "recurrent, transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitation, feeling of anxiety, and sometimes followed by chills." When hot flushes occur at night, they are often called night sweats.

68 Fed.Reg. at 17955. This artificially and arbitrarily narrow interpretation of "vasomotor symptoms associated with the menopause" is both inaccurate from a medical perspective and inconsistent with medical practice in the treatment of symptomatic menopausal women. Declaration of Alan Altman, MD ("Altman Decl.") at ¶ 7; Declaration of Gloria M. Bachmann, MD ("Bachmann Decl.") at ¶ 9; Declaration of James A. Simon, MD ("Simon Decl.") at ¶ 6; Declaration of Ronald L. Young, MD ("Young Decl.") at ¶ 3. Accordingly, in assessing the effectiveness of the Estratest® products, the Agency may not limit consideration to effectiveness in treating "hot flushes" and "night sweats" and, indeed, must consider evidence relating to the original indication for which the DESI Panel and FDA concluded that estrogen-androgen combination products were effective, *i.e.*, the menopausal syndrome.

"Vasomotor symptoms" encompass more than hot flushes and night sweats; they also include the menopausal symptoms of palpitations, headache, and fatigue. Altman Decl. at ¶ 7. Moreover, when physicians and patients assess the effectiveness of therapy used to relieve vasomotor symptoms, they look at an interrelated constellation of symptoms which consists of

hot flushes, night sweats, sleep dysfunction, fatigue, lack of energy, irritability, sleeplessness, mood changes, and a general decline in sense of well-being. Altman Decl. at ¶ 7; Bachmann Decl. at ¶ 9; Simon Decl. at ¶ 6; Young Decl. at ¶ 3. Further, there is a "cascade effect" from menopausal symptoms: for example, night sweats can disrupt sleep, leaving a woman feeling tired and irritable during the day. Altman Decl. at ¶7; Young Decl. at ¶ 3. Accordingly, the appropriate indication for FDA to consider in this proceeding is treatment of the entire menopausal syndrome, including vasomotor and associated symptoms, an indication for which the Estratest® products are clearly more effective than estrogen alone in many patients.

b. FDA Does Not Question The Effectiveness Of The Estratest® Products For Treatment Of Vasomotor Symptoms

In the Notice, FDA does not question that the Estratest® products are effective for treatment of vasomotor symptoms. To the contrary, the Agency states that it is proposing to reclassify estrogen-androgen combination products as lacking substantial evidence of effectiveness on the basis that "for this indication there is not substantial evidence of the contribution of each component to the effectiveness of these combination drugs." 68 Fed.Reg. at 17953 (emphasis added). See also id. at 17955 ("FDA believes that substantial evidence is lacking that the addition of an androgen can improve the effectiveness of estrogen alone in the treatment of vasomotor symptoms (i.e., hot flushes)"). Thus, FDA's Notice is premised solely on the requirements of the so-called "combination drug policy," which requires that, for fixed combination dosage form prescription drugs for human use, "each component make[] a contribution to the claimed effects." 21 C.F.R. § 300.50(a).

c. The Estratest® Products Meet The Requirements Of The Combination Policy

The Estratest® products meet the requirements of FDA's combination drug policy. First, as noted above, the regulation specifically provides that combination drugs subject to a DESI "effective" classification are considered to be in compliance with combination drug policy. 21 C.F.R. § 300.50(c) ("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"). Thus, the Estratest® products must be deemed to be in compliance with the combination policy on the basis that they are subject to the 1972/1976 DESI effective classification for estrogen-androgen fixed combination products.

Further, as set forth below, the available data also demonstrate that the Estratest® products meet the requirements of the combination policy. As described fully in Section IV.B.2.d.ii., below, when medically acceptable doses of estrogen alone do not provide adequate relief of vasomotor and associated symptoms, many patients may be able to obtain adequate relief by taking the Estratest® estrogen-androgen combination. Significantly, the estrogen-androgen combination enables these patients to obtain adequate relief while maintaining or even lowering their estrogen dose and thereby generally avoiding the dose-dependent adverse reactions associated with escalating doses of estrogen and generally without causing any androgen-related adverse effects. This showing is supported by substantial evidence consisting of adequate and well-controlled clinical investigations.

Importantly, however, the courts have recognized that the showing necessary to satisfy the Agency's combination drug policy is not required to meet the "substantial evidence"

standard. E.R. Squibb & Sons, Inc. v. Weinberger, 483 F.2d 1382, 1385 (3rd Cir. 1973); Edison Pharm. Co., Inc. v. FDA, 600 F.2d 831, 840-841 (D.C. Cir. 1979). This is because the combination drug policy is based on safety, not efficacy, considerations and because the "substantial evidence" standard, and concomitant requirement for adequate and well-controlled clinical investigations, applies only to proof of efficacy – which FDA acknowledges exists in the case of estrogen-androgen combinations.

Further, under Section 505(d) of the Act, "substantial evidence" is defined to be evidence upon which experts qualified by scientific training and experience can fairly and responsibly conclude support the effectiveness of the drug product at issue for its labeled conditions of use. 21 U.S.C. § 355(c). In this case, as evidenced by the attached declarations, qualified experts have concluded that the available scientific data fairly and responsibly support the medical rationale of the combination Estratest® products and their safety and effectiveness for the labeled indication. Altman Decl. at ¶ 3; Bachmann Decl. at ¶ 5; Lobo Decl. at ¶ 3; Simon Decl. at ¶ 4; Young Decl at ¶¶ 5, 7.

d. The Estrogen-Androgen Combination Is Medically And Scientifically Rational

i. The Formulation Of The Estratest® Products Is Based On The Long-Standing And Well-Documented Medical And Scientific Understanding Of The Role Of Estrogen And Androgen In The Management Of The Menopausal Syndrome

The menopause (natural or surgical) is an important physiological event in a woman's life. Currently, about 40 million American women are menopausal. The average age of natural menopause is about 51 years, and the average woman who reaches the menopause will probably

live another 30 or more years. Thus, management of the menopause, like that of aging in general, is a medical and social issue of growing importance.

The use of hormone replacement therapy to treat menopausal symptoms began more than 70 years ago. Estrogen was first synthesized in the 1920's[3] and the use of estrogenic hormones for the relief of menopausal disturbances was well established as a part of daily practice by 1941.[4,5,6] Similarly, having been synthesized in 1935, androgens were first used for the clinical management of menopausal symptoms in 1936 by Mocquot and Moricard, who treated bilaterally oophorectomized women with male sex hormone for their climacteric symptoms.[7] In 1942 Greenblatt[8] noted that testosterone not only relieves hot flushes but also may restore sexual libido. Refinement of estrogen and androgen therapy in the menopausal patient was discussed by Geist and Salmon.[9] As Dr. Lobo explains in his attached declaration:

> The rationale of combining estrogen and androgen for use in treating menopausal symptoms emerged in the 1940's and was based upon data which indicated that certain menopausal women exhibited androgen, as well as estrogen, deficiency and that in this population estrogen-androgen combination products could provide relief of menopausal symptoms not adequately controlled on estrogen alone.

Lobo Decl. at ¶ 5.

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[3] Doisy E, Veler C, Thayer S. Folliculum from urine of pregnant women. Am J Physiol 1929; 90:329-30.

[4] Hawkinson LF. JAMA 1938; 111:390.

[5] Schneider PF. Am J Obstet Gynecol 1939; 37:861.

[6] Berlind M. M Rec 1941; 153:54.

[7] Mocquot P, Moricard R. Action de l'hormone mâle (acétate de testostérone) dans les troubles de la castration chez la femme. Bull Soc d' obstet et gynec. 1936; 25:787-790.

[8] Greenblatt RB. Androgenic therapy in women. J Clin Endocrinol Metab 1942; 2:665-6.

[9] Geist SH, Salmon UJ. Androgen Therapy in Gynecology. JAMA 1941; 117:2207.

In the 1950s, numerous reports began to appear in the literature that described the effectiveness of estrogen-androgen combination therapy for improving the overall feeling of well-being, energy level, libido, and quality of life in postmenopausal women. In 1950, Greenblatt *et al*[10] studied the efficacy and safety of a number of androgenic formulations in menopausal women in a double-blind, crossover manner. The published report of that study indicates that the estrogen-androgen combination provided the same complete relief of menopausal symptoms as estrogen alone, with 66.6 per cent of patients stating a preference for the combination due to increased "well being." Vaginal bleeding using the combination was considerably less in amount than reported by the same patients using estrogen alone. The combination was reported to have significantly lower incidence and diminished amount of breast turbidity, pelvic congestion, and nausea, and a greater incidence of increased libido. Increased libido was reported by 23.5% of patients taking the combination, versus 12.3% of those treated with diethylstilbestrol alone. The 1950 Greenblatt study is included in the Point-by-Point analyses of adequate and well-controlled clinical investigations in Volume 3.

The beneficial effect of testosterone on menopausal symptoms was also reported by Glass[11] in 1950. Birnberg and Kurzrok[12] evaluated the responses to an estrogen-androgen combination containing 0.001 mg/d ethinyl estradiol plus 1 mg/d methyltestosterone administered for various periods to 61 menopausal or postmenopausal women. They reported

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[10] Greenblatt RB, Barfield WE, Garner JF. Evaluation of an estrogen, androgen, and estrogen-androgen combination, and placebo in treatment of menopause. J Clin Endocrinol Metab 1950; 10:1547-58.

[11] Glass SJ. The advantages of combined estrogen-androgen therapy of the menopause. Clin Endocrinol 1950; 10:1616-17.

[12] Birnberg CH, Kurzrok R. Low-Dosage androgen-estrogen therapy in the older age group. J Am Geriatric Soc 1955; 3.

that in addition to exerting a general increase in alertness and responsiveness, this therapy brought about favorable personality changes. The patients lost their former irritability, nervousness, and sense of fatigue, and most reported increased libido. A description of the early key studies can be found in Table 1.

Table 1. Early Key Studies

Investigators/ Year	Study Design	Number Of Subjects / Drug Combinations	STUDY SUMMARY
Geist, S.H. Salmon,U.J., 1941	Prospective case series	422 subjects testosterone propionate 25 mg twice weekly (IM)	RELIVED MENOPAUSAL SYMPTOMS IN A SUBSET OF MENOPAUSAL WOMEN
Greenblatt, R.B. Barfield, W.E. Garner, J.F., 1950	Prospective, double-blind, placebo controlled	31 subjects methyltestosterone 5 mg/day plus diethylstilbestrol 0.25 mg/day (Oral)	IMPROVED MENOPAUSAL SYMPTOMS, WELL-BEING AND LIBIDO
Glass, S.J., 1950	Prospective, double-blind, placebo controlled	92 subjects methyltestosterone 5 mg/day plus diethylstilbestrol 0.25 mg/day (Oral)	"SMOOTHER TRANSITION WITH NORMAL CHANGES INCIDENT TO THE MENOPAUSE"
Birnberg, C.H. Kurzrok, R., 1955	Prospective case series	70 subjects methyltestosterone 1 mg/day plus ethinyl estradiol 0.001 mg/day (Oral)	"FAVORABLE PERSONALITY CHANGES" WITH REDUCED "IRRITABILITY, NERVOUSNESS, AND SENSE OF FATIGUE"

A 1985 study by Sherwin and Gelfand[13] is described by the FDA in its April 14, 2003 Federal Register Notice as follows:

> An early randomized, placebo-controlled, five-arm, two-period crossover clinical trial by Sherwin and Gelfand [reference omitted] compared the effects on surgically menopausal women of immediate postoperative parenteral administration of estrogen alone (n=11), androgen alone (n=10), estrogen and androgen in combination (m=12), and placebo (n=10) to hysterectomy controls (n=10) and found that the androgen alone, estrogen-androgen combination, and control hysterectomy groups had lower (i.e., lower frequency and severity) menopausal somatic symptoms scores than the estrogen alone and placebo groups. The menopausal somatic symptoms score evaluated a constellation of symptoms including hot flushes, cold sweats, weight gain, rheumatic pains, cold hands and feet, breast pains, headaches, numbness and tingling, and skin crawls.

68 Fed. Reg. at 17955. Indeed, in this study, during both treatment phases, the somatic symptom scores for the estrogen-androgen, androgen-alone and control hysterectomy groups were lower than those of the estrogen-alone and placebo groups ($p<0.01$). In addition, women in the estrogen-alone and placebo groups had significantly lower ratings as to energy level and well-being than the control group with intact ovaries, the androgen-alone group, or the estrogen-androgen combination group in the three treatment months of both phases of the study ($p<0.01$) and in treatment months 1, 3, 5, 6 and 7 ($p<0.01$). The psychological symptom scores of the estrogen-alone and placebo groups were significantly higher than those of the estrogen-androgen, androgen-alone and control hysterectomy groups during both treatment phases ($p<0.01$). Also, the composite scores of all items on the menopausal index of the estrogen-androgen, androgen-alone and control hysterectomy groups were lower than the estrogen-alone and placebo groups

[13] Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or administration in the surgical menopause. Am J Obstet Gynecol 1985; 151:153-60.

($p<0.01$). This study thus clearly demonstrates the contribution of the androgen component in the treatment of menopausal symptoms. This Sherwin and Gelfand study is included in the Point-by-Point analyses of adequate and well-controlled clinical investigations attached hereto in Volume 3.

In the April 14, 2003 Notice, FDA provides no explanation for why it would not regard this Sherwin and Gelfand study as demonstrating the contribution of androgen to estrogen-androgen therapy for the DESI-effective indications. If it has discounted the relevance of this study because it measured a "constellation of symptoms" instead of focusing solely on "hot flushes," this is contrary to the appropriate medical interpretation of both the initial and current DESI-effective indications. See Sections IV.B.2.a. above and IV.B.2.d.iii(a) below.

Over the past 68 years, a large body of clinical data has been developed on the use of various estrogen-androgen combination regimens in the treatment of a range of menopausal symptoms. This body of data uniformly supports the safety and efficacy of these combinations and the rationale for using them in the management of manifestations of the menopausal syndrome, *i.e.*, vasomotor and related symptoms, in individuals whose symptoms are not adequately controlled by estrogen supplementation alone. This conclusion is supported by the opinion of preeminent experts in the study and use of hormone replacement therapy in the menopausal woman:

> Consistent with my understanding of the published relevant clinical, biological, case control, pharmacokinetic, and observational database, and reinforced by my extensive experience with the Estratest® estrogen-androgen combination products, I have found that a significant number of patients who are not sufficiently responsive to estrogen alone, or who have had relapse of symptoms, can achieve control of their vasomotor and associated symptoms by judicious use of Estratest® HS or

> Estratest®. Indeed, approximately 90 percent of this population responds to **nothing but** the Estratest® estrogen-androgen combinations and are able to maintain control without significant estrogen or androgen adverse reactions. More importantly, this combination estrogen-androgen therapy frequently enables me to **lower** the prescribed oral estrogen dose, consistent with current treatment paradigm, while gaining and maintaining control over previously unresponsive vasomotor and associated symptoms. The estrogen-androgen combination does this by lowering the elevated SHBG and allowing more bioavailable hormone to be successfully utilized.

Altman Decl. at ¶ 6. Based on these data, it is apparent that the use of Estratest® products for their labeled indications is both medically and scientifically rational.

ii. The Rationale For Use Of Estrogen-Androgen Combinations In Managing Menopausal Symptoms Is Further Supported By Data Establishing The Pharmacokinetic Effects Of Including Androgen With Estrogen In Hormone Replacement

Extensive clinical testing has shown that Estratest® and Estratest® HS administration produce relatively low circulating levels of methyltestosterone, in the range of 20 to 30 ng/dl.[14] Because methyltestosterone is at least as potent as testosterone,[15] some androgenic biological effect would be expected to result from this factor alone. However, it is apparent that an equally significant pharmacologic effect of methyltestosterone may be contributed by the fact that it suppresses sex hormone binding globulin (SHBG).

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[14] Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses. J Repro Med 1998; 43:847-56.

[15] Myers LS, Dixen J, Morrissette D, Carmichael M, Davidson JM. Effects of estrogen, androgen, and progestin on sexual psychophysiology and behavior in postmenopausal women. J Clin Endocrinol Metab 1990; 70:1124-31.

SHBG is a glycoprotein that is synthesized and secreted by the liver, circulates in the blood and has a high binding affinity for a number of androgens and estrogens.[16,17,18] SHBG binding prevents sex steroids from entering cells, thereby modulating the activities of the circulating hormones and their metabolism.[19] Approximately 66% of testosterone in women is bound to SHBG, a significantly larger proportion than in men.[20] Additionally, SHBG also binds estradiol. The plasma levels of SHBG determine the bioactive fraction of sex hormones (testosterone and estradiol). Reduction in circulating levels of SHBG by exogenous testosterone is well documented.[21,22] Other things being equal, the concentration of bioavailable testosterone and estradiol in circulation should increase if the SHBG level decreases.

Accordingly, the hypothesis that the therapeutic benefit of the addition of methyltestosterone to esterified estrogens may in part be attributable to its action on circulating levels of SHBG was tested in two recent studies comparing the effects of Estratest® HS (S0303103), Estratest® (S0302101), and Estratab® (esterified estrogens) (both studies) on

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[16] Rosner W. The functions of corticosteriod-binding globulin and sex hormone-binding globulin: recent advances. Endocr Rev 1990; 11:80-91.

[17] Anderson DC. Sex-hormone-binding globulin. Clin Endocrinol (Oxf) 1974; 3:69-96.

[18] Dunn J, Nisula B, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteriod-binding in human plasma. J Clin Endocrinol Metab 1981; 53:58-68.

[19] Siiteri PK, Murai JT, Hammond GL, Nisker JA, Raymoure WJ, Kuhn RW. The serum transport of steroid hormones. Recent Prog Horm Res 1982; 38:457-510.

[20] Id.

[21] Plymate SR, Leonard JM, Paulsen CA, Fariss BL, Karpas AE. Sex hormone-binding globulin changes with androgen replacement. J Clin Endocrinol Metab 1983; 57:645-8.

[22] Shifren JL, Braunstein GD, Simon JA, *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000; 343:682-8.

sexual function in postmenopausal women.[23] While similar in some design features, the two studies differed in the study population and in the dosages of study drugs. S0303103 randomized naturally and surgically menopausal women and the mean age of the two treatment groups was 53 and 54 years, respectively. On the other hand, S03032101 randomized patients who were surgically menopausal and whose mean age was somewhat younger than those in S0303103. The total daily dosages of the combination of methyltestosterone and esterified estrogens and the dosage of esterified estrogens administered was also different. Hormone level measurements including total testosterone, bioavailable and free testosterone, total estradiol, bioavailable and free estradiol, and SHBG were performed in both studies. The hormone concentration results are given for both studies in Tables 2 and 3.

[23] These studies were submitted to IND 41744.

Table 2. Mean Change from Baseline in Serum Hormone Concentrations after Administration of Estratest®H.S. and Estratab®: Protocol S0303103

	Estratest® HS	Estratab® 0.625 mg	P-Value for treatment difference*
Total testosterone (ng/dL) normal menopausal range: 7-40			
Baseline	18.9±9.1	20.8±11.1	
Δ from BL (endpoint)	-3.7±6.8	-0.1±7.2	0.020
(95% Confidence Intervals))	(-5.6, -1.8)	(-1.9, 1.7)	
P value for Δ from BL*	<0.010	0.905	
Bioavailable testosterone (pg/ml) normal range (female): 1.1-4.3			
Baseline	2.7±1.5	3.1±2.7	
Δ from BL (endpoint)	2.0±2.0	-0.3±2.4	<0.010
(95% Confidence Intervals))	(1.4, 2.5)	(-0.9, 0.2)	
P value for Δ from BL*	<0.010	0.264	
SHBG (nmol/L) normal range: 28-112			
Baseline	160.6±91.4	164.7±99.8	
Δ from BL (endpoint)	-104.2±80.3	-18.2±76.7	<0.010
(95% Confidence Intervals))	(-123.1, -85.3)	(-36.1, -0.2)	
P value for Δ from BL*	<0.010	0.053	
DHEA-S (μg/dL) normal range: 20-157			
Baseline	60.3±32.1	63.7±35.6	
Δ from BL (endpoint)	2.3±17.6	-0.6±20.7	0.357
(95% Confidence Intervals))	(-2.6, 7.2)	(-5.2, 4.0)	
P value for Δ from BL*	0.312	0.806	
Androstenedione (ng/dL) normal range: 30-120			
Baseline	63.3±25.2	67.3±24.6	
Δ from BL (endpoint)	-9.6±47.0	3.1±32.6	0.112
(95% Confidence Intervals))	(-8.7, 5.1)	(-8.7, 4.6)	
P value for Δ from BL*	0.133	0.459	
Total estradiol (ng/dL) normal range in menopause: <1.5 ng/dL			
Baseline	3.6±3.5	3.4±2.5	
Δ from BL (endpoint)	-1.7±5.6	-1.6±4	0.112
(95% Confidence Intervals))	(-2.0, 0.10)	(-0.7 ,1.3)	
P value for Δ from BL*	<0.133	0.459	
Estrone (ng/dL) normal range in menopause: <4.0 ng/dL			
Baseline	9.4±7.3	9.4±9.6	
Δ from BL (endpoint)	-1.1±8.1	3.5±10.4	<0.010
(95% Confidence Intervals))	(-3.3, 1.2)	(1.3, 5.7)	
P value for Δ from BL*	0.306	0.010	

*P-values obtained from an ANOVA

Values are mean±SD; Δ=change from; BL=baseline; Wk=week; CI=confidence interval

Note: Endpoint is defined as the last non-missing post-baseline evaluation through 30 days after discontinuation of study medication.

Table 3. Mean Change from Baseline in Serum Hormone Concentrations after Administration of Estratest® and Estratab®: Protocol S0302101

Parameter	Statistic	Estratest® (N=51)	Estratab® 1.25 mg (N=49)	p-value[2]
Total estradiol (ng/dL)	N	43	47	0.054
	Mean (SD)[3]	-1.13 (2.26)	0.06 (3.13)	
	p-value[1]	0.002**	0.900	
Free estradiol (pg/mL)	N	40	44	0.002**
	Mean (SD)	0.42 (0.71)	-0.02 (0.56)	
	p-value[1]	<0.001**	0.850	
Bioavailable estradiol (ng/dL)	N	42	47	<0.001**
	Mean (SD)	1.13 (2.12)	-0.03 (1.04)	
	p-value[1]	0.001**	0.834	
Estrone (ng/dL)	N	44	47	0.010**
	Mean (SD)	-10.30 (18.76)	-0.08 (16.76)	
	p-value[1]	<0.001**	0.974	
Total testosterone (ng/dL)	N	48	46	0.823
	Mean (SD)	-7.84 (9.31)	-6.06 (36.88)	
	p-value[1]	<0.001**	0.271	
Free testosterone (pg/mL)	N	48	45	<0.001**
	Mean (SD)	1.04 (0.78)	-0.17 (1.48)	
	p-value[1]	<0.001**	0.442	
Bioavailable testosterone (ng/dL)	N	48	44	<0.001**
	Mean (SD)	2.70 (2.06)	0.07 (1.04)	
	p-value[1]	<0.001**	0.646	
SHBG (nmol/L)	N	49	47	<0.001**
	Mean (SD)	-140.5 (85.2)	1.8 (72.3)	
	p-value[1]	<0.001**	0.868	

* Significant at the 0.050 level. ** Significant at the 0.010 level.

[1] P-values computed using a paired t-test.

[2] P-values for the Estratest® versus Estratab® treatment groups at Endpoint are based on an ANOVA model with effects for treatment group and pooled center.

[3] Mean change from baseline at study endpoint.

Note: Endpoint is defined as the last non-missing post-Baseline evaluation collected through 30 days after discontinuation of study medication.

Endocrine data from both of these studies demonstrated that subjects treated with Estratest® (1.25 mg esterified estrogens, 2.5 mg methyltestosterone) compared to those receiving Estratab® (1.25 mg esterified estrogens) showed significantly ($p<0.010$) decreased

levels of SHBG and total testosterone and increased the levels of bioavailable testosterone. Furthermore, weakly bound estradiol and bioavailable estradiol increased, the change from baseline reaching significance in Study S0302101. These observations show that Estratest® therapy raises the bioavailable fraction of estrogen and testosterone in the blood either by decreasing circulating SHBG or by inhibition of hormone-SHBG-binding by methyltestosterone, or both.

Ovarian and adrenal androgens decrease with age due to reduced production rates. Ovarian estrogen and androgen levels are reduced to a greater degree after surgical menopause, compared to natural menopause levels. Although the metabolic pathways of androgen remain unchanged, there is a marked increase in aromatization of endogenous testosterone to estradiol in peripheral tissues. Because of the presence of androgen receptors throughout the body, the androgen decline can affect many physiological processes in menopausal women. Surgically menopausal women are commonly prescribed estrogen replacement therapy to minimize the effects of decreased estrogen production on menopausal symptoms, including vasomotor and related symptoms and bone mineral density. Endogenous androgen bioavailability may be further reduced in these patients due to the increase in SHBG levels associated with oral estrogen replacement therapy. Thus, hormonal data from Studies S0303103 and S0302101 provide an understanding of the effects of the Estratest® products on the endocrine environment of naturally and surgically postmenopausal women.

Based in part on these findings, the preeminent experts whose declarations are included with this submission concur that the increase in bioavailable estradiol associated with methyltestosterone treatment explains why the combination of methyltestosterone and esterified

estrogens is uniquely effective in improving menopausal symptoms previously refractory to an equivalent dose of estrogens alone. For instance, Dr. Simon stated:

> In this menopausal population with residual vasomotor symptoms on estrogen therapy alone, the beneficial effects of the estrogen/androgen combination products of decreasing SHBG levels has the potential added benefit of enabling the patient to obtain adequate relief of her vasomotor and associated symptoms without increasing the estrogen dose and possibly even lowering the estrogen dose and thereby enhancing the safety of menopausal therapy. In this respect, it is worth noting that the fact that the combination results in more bioavailable estradiol does not translate into an increased risk of dose-dependent side effects because, under such circumstances, total estrogen levels are actually reduced as free estradiol is either taken up by receptor sites or metabolized and cleared from the body. The effect of increasing bioavailable estradiol is to allow a woman's biological system to work more efficiently by increasing both receptor activity and clearance i.e., the body is better able to use what it needs and discard what it does not need.

Simon Decl. at ¶ 11. Similarly, Dr. Altman explained:

> The Estratest® estrogen-androgen combination products frequently control these vasomotor and associated symptoms in cases where estrogen therapy alone has been unsuccessful or even contributes to the problem by creating a hormonal imbalance by increasing SHBG levels and thereby reducing bioavailable estrogen and androgen. In these androgen deficient women, the estrogen-androgen combination products can help to restore the natural hormonal balance and thereby relieve vasomotor and associated symptoms. While the results are especially dramatic in women who have had a hysterectomy and bilateral oophorectomy, estrogen-androgen combination products can produce equally dramatic results in naturally menopausal women who have a significant androgen deficiency due to over-prescribing of oral estrogen or an adrenal deficiency. Indeed, many patients have told me that the Estratest® products have dramatically improved their lives.

Altman Decl. at ¶ 8. Both the relevant data and expert opinion therefore demonstrate that use of the Estratest® products for their labeled indications is medically and scientifically rational.

iii. Clinical Data, Including Data From Adequate And Well-Controlled Clinical Trials, Demonstrate The Effectiveness Of The Estratest® Combinations In The Management Of Symptoms Of The Menopausal Syndrome Under Both The Original And The Revised DESI-Effective Indication Statements

(a) The Menopausal Syndrome

The menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. For several years before normal menopause, estradiol and progesterone production decline despite the occurrence of ovulatory activity.[24] This waning of ovarian follicular activity reduces the negative feedback inhibition of estradiol and inhibin on the hypothalamic-pituitary system, resulting in a gradual rise in follicle-stimulating hormone (FSH). The remaining ovarian follicles are increasingly those less responsive to FSH. The menopause occurs when the residual follicles are refractory to elevated concentrations of FSH. Estradiol levels remain relatively unchanged or tend to rise with age until the onset of the transition and are usually well preserved until the late perimenopause, presumably in response to the elevated FSH levels. Concentrations of testosterone have been reported to fall by about 50% during reproductive life, between the ages of 20 and 40. They change little during the transition and, after the menopause, may even rise.[25] The loss of hormone production can cause both acute and chronic consequences in hormone-dependent tissues such as the brain, bones, heart, blood vessels, and skin.

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[24] Sherman BM, West JH, Korenman SG. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. PG. J Clin Endocrinol Metab 1976; 42.

[25] Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. Recent Prog Horm Res 2002; 57:257-75.

As explained above in Section IV.B.2.a., the menopausal transition is associated with a complex of interrelated symptoms. These include somatic, or physical, effects such as hot flushes, night sweats, vaginal dryness, palpitations, and micturition complaints, as well as associated psychosomatic or psychological effects such as fatigability, insomnia, irritability, decreased libido, nervousness, depression, anxiety, and lack of concentration. As described by the experts whose declarations accompany this submission, these effects are not all necessarily direct results of the hormonal changes associated with the menopause but are nevertheless part of a cascade of symptoms interrelated to each other and thus causally linked. See Altman Decl. at ¶ 7; Bachmann Decl. at ¶ 9; Simon Decl. at ¶ 6; Young Decl. at ¶ 3.

For these reasons, the experts find no scientific or medical rationale or justification for FDA's 1976 revision of the DESI-effective indication for estrogen-androgen combination drug products, except when interpreted in light of the added parenthetical clarifying that hormone replacement has not been shown to be effective in the treatment of nervous conditions or depression that may be associated with the menopause. Excluding those conditions, which are conceded not to be directly related to or treated by changes in hormone levels, the experts nevertheless believe that the scope of the term "vasomotor symptoms" used in the revised DESI-effective indication statement includes more than just hot flashes or flushes. Rather, the experts conclude that the revised indication statement continues to subsume the constellation of somatic and psychosomatic symptoms classically associated with the menopausal syndrome, and that data showing the effects of the combination on that entire range of symptoms is properly relied on to support the indication for the product as currently or previously worded under its DESI-

effective classifications. See Altman Decl. at ¶ 7; Bachmann Decl. at ¶ 9; Simon Decl. at ¶ 6; Young Decl. at ¶ 3.

(b) Clinical Trials Of The Estrogen-Androgen Combination Products, Prospectively Designed And Conducted For Purposes Other Than Re-Establishing The Validity Of The FDA's Long-Standing DESI-Effective Classification Of Those Products, Provide Sufficient Data To Support The Products' Existing Indication For Use

Extensive investigations have been conducted of the contribution of androgen to the effectiveness of combination estrogen-androgen drug products. Indeed, Solvay has conducted nine clinical trials in which Estratest® and Estratest® HS were compared to Estratab® 1.25 mg, Estratab® 0.625 mg, and conjugated equine estrogens (CEE, Premarin®, 1.25 mg). Eight (8) of the studies discussed herein were designed and initiated before the FDA published its "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women" in 1995, advising pharmaceutical manufacturers of desired standards for study design. The ninth, study S0303103, was initiated in 1998.

All of these clinical trials were designed and conducted as post-marketing studies and were never components of a clinical development program. They are part of an ongoing investigation into the use of Estratest® and Estratest® HS in women for conditions associated with the menopause, but were not specifically designed or intended to generate pivotal clinical data in support of a product approval application or otherwise to re-prove the basic conclusions underlying the long-standing DESI-effective classification of estrogen-androgen combination

drug products. Nevertheless, these studies do provide data adequate to support that classification.

Table 4 provides details of the nine clinical studies of the Estratest® products that addressed menopausal/vasomotor symptoms. The assessment of treatment in relieving menopausal symptoms was either a primary or secondary objective of these studies. The treatment duration ranged from 8 weeks to 2 years. The nine studies included: one open label, parallel study (Protocol 030.0.12); three double blind, placebo-controlled, parallel studies (Protocols EST-1, 030.0.0702, 030.0.13); and five double-blind, parallel studies (Protocols EST-2, EST-3, 030.0.10, 030.8.01, S0303103). Of the total 859 patients in these nine studies, 382 were randomized to receive Estratest®; 244 to Estratab®; 172 to receive Premarin® treatment; and 51 to the placebo treatment group.

Table 4. Overview of Estratest® Controlled Clinical Studies in Menopausal Symptoms

PROT. NO.	PRINCIPAL INVESTIGATORS / YEAR	STUDY DESIGN	CLINICAL ENDPOINTS	DOSE DURATION	NUMBER OF SUBJECTS /PER GROUP	MENOP. STATUS	NO. OF CTRS	CLINICAL REPORT NUMBER
EST-1[26]	Andrews; Young 1993	Double-blind, placebo controlled, parallel	VMS, Lipids, Psychometric	12 weeks	N=12 Estratest®=5 Estratab® 1.25 mg=3 Placebo=4	Surgical	2	400.009
EST-2	Watts *et al* 1992	Double-blind, parallel	VMS, BMD, Lipids, VC, Psychometric	2 years	N=66 Estratest®=33 Estratab® 1.25mg=33	Surgical	4	N/A
EST-3[27]	Speroff 1992	Double-blind, Parallel	VMS, Lipids, QL, BB, EH, VC	6 months	N=26 Estratest®HS=13 Estratab® 0.625mg=13	Natural	1	30.00.001
030.0.0702	Simon; Klaiber; Bowen, 1999	Double-blind, placebo controlled, parallel	VMS, QL, Mood, Psychometric, Androgen Levels	12 weeks	N=92 Estratest®HS=19 Estratest®=18 Estratab® 0.625mg=17 Estratab® 1.25mg=19 Placebo=19	Natural	3	200.0118
030.0.10	Sarrel, 1995	Double-blind, parallel	VMS, Blood Flow #, FSF, QL, VC	8 weeks	N=20 Estratest®=9 Estratab® 1.25mg=11	Natural	1	200.0122
030.0.12	Raisz; Schwartz; Bowen, 1995	Open label, parallel	VMS; Bone Markers	9 weeks; Calcium** (1500 mg/day)	N=40 Estratest®=13 Estratab® 1.25mg=12 Premarin® 1.25mg=15	Natural or Surgical	3	200.0115
030.0.13	Bachmann *et al* 1998	Double-blind, placebo controlled, parallel	VMS, QL, FSF, Psychometric Hormone profile, Lipids	16 weeks	N=79 Estratest®=25 Estratab® 1.25mg=26 Placebo=28	Surgical	10	200.0125
030.8.01[28]	Appel, Bachmann; Barrett-Connor *et al* 1997	Double-blind, parallel	VMS, QL, BMD	2 years; (daily calcium**)	N=311 Estratest®HS=81 Estratest®=73 Premarin® 0.625mg=79 Premarin® 1.25mg=78	Surgical	25	400.015
S0303103	Lobo; Bachmann; Baker *et al* 2002	Double-blind, parallel	MSIQ BISF-W	16 weeks + (2 wk lead-in)	N=218 Estratest®HS=107 Estratab®0.625 mg=111	Natural and Surgical	20	200.0154

Legend: BB = Breakthrough Bleeding
BISF-W = Brief Index of Sexual Functioning in Women
BMD = Bone Mineral Density
CSFQ = Changes in Sexual Functioning Questionnaire
EH = Endometrial Histology
FSF = Female Sexual Function
MSIQ = Menopause Sexual Interest Questionnaire
** Oscal®
QL = Quality of Life
SES = Sexual Energy Scale
VC = Vaginal Cytology
VMS = Vasomotor Symptoms
# Fingertip urethra, vagina

[26] The study report for this study is attached hereto in Volume 18.
[27] The study report for this study is attached hereto in Volume 19.
[28] The study report for this study is attached hereto in Volume 20.

(c) Short Term Solvay Studies

Two of the seven studies discussed in this section were of less than 12-week duration: Sarrel study 030.0.10 (eight-week duration) and Raisz study 030.0.12 (nine-week duration). Two of the studies (Andrews study EST-1, and Simon study 030.0.0702) are 12-week studies; two (Bachmann study 030.0.13 and Lobo study S0303103) are 16-week studies; and one (Speroff study EST-3) is a 6-month study. Three of the seven studies (Andrews EST-1, Simon 030.0.0702, and Bachmann 030.0.13) were placebo controlled. Four of the six studies (Andrews EST-1, Raisz 030.0.12, Bachmann 030.0.13, and Sarrel 030.0.10) compared Estratest® to Estratab® 1.25mg, while two (Speroff EST-3 and Lobo S0303103) compared Estratest® HS to Estratab® 0.625 mg. The Simon study 030.0.0702 compared both strengths of Estratest® to two strengths of Estratab® and a placebo. The Simon study is also one of the six which were double-blinded. The other five double blind studies were Andrews EST-1, Speroff EST-3, Sarrel 030.0.10, Bachmann 030.0.13 and Lobo S0303103. The Raisz study 030.0.12 had an open label design.

A total of 491 postmenopausal women were randomized to treatment in the seven short-term studies. Of those, 70 patients were randomized to Estratest® (in five studies), 138 patients to Estratest® H.S. (in three studies), 227 patients to Estratab® (all seven studies), and 51 patients to placebo (in three studies). Of the 491 patients randomized to treatment collectively in these seven studies, a total of 434 (88.3%) patients completed the trials. Two of the studies (Speroff EST-3 and Sarrel 030.0.10) had a 100% completion rate.

The majority of patients enrolled in these studies were naturally menopausal. Two of the studies (Andrews EST-1 and Bachmann 030.0.13) examined only surgically menopausal women. For this reason, patients were younger in these two than in the other four studies. All of the

studies except Andrews EST-1 examined a study population which was mostly Caucasian. Study Andrews EST-1 consisted of 33.3% each Caucasian, Hispanic and Black.

The results of the seven short-term studies examined in this section as a group are summarized in Table 5.

Table 5. Results of Short- and Long-Term Studies Assessing Menopausal Symptoms

Study	Measurement	Treatments (N)	Effect on Menopausal Symptoms
Short-term studies			
Andrews EST-1 1993	Menopausal symptom scale, Patient diary, Hopkins Symptom Checklist	Estratest®(5), Estratab® 1.25 mg(3), Placebo(4)	No interpretation possible because recruitment goals of study not met
Speroff EST-3 1992	Menopausal symptom scale	Estratest® H.S.(13), Estratab® 0.625(13)	Estratest®H.S. and Estratab® 0.625mg were comparable
Simon 030.0.0702 1999	Menopausal symptom scale	Estratest® H.S.(19), Estratest® (18), Estratab® 0.625 mg (17) Estratab® 1.25 mg (19), Placebo® (19)	ESE/M HS, ESE/M, and Both ESE groups showed some effectiveness in treating somatic symptoms. ESE/M HS, ESE/M and ESE HS but not ESE showed some effectiveness in the treatment of psychosomatic symptoms. None of the treatments was effective in treating psychological symptoms
Sarrel 030.0.10 1995	Menopausal symptom scale	Estratest® (9), Estratab® 1.25 mg (11)	Estratest®H.S. and Estratab® 0.625mg were comparable
Raisz 030.012 1995	Menopausal symptom scale	Estratest® (13), Estratab® 1.25 mg (12), Premarin® 1.25 mg (15)	Estratest® significantly relieved somatic, psychosomatic and psychological symptoms compared to the estrogen-only groups, which significantly relieved only somatic symptoms.
Bachmann 030.013 1998	Menopausal symptom scale, Patient diary, Greene Climacteric scale	Estratest® (25), Estratab® 1.25 mg (26), Placebo(28)	Estratest®H.S. and Estratab® 0.625mg were superior to placebo, but comparable to each other
Lobo S0303103 2002	Menopause-Specific Quality of Life Scale Questionnaire	Estratest® H.S. (106), Estratab® 0.625 mg (110)	Estratest®H.S. and Estratab® 0.625mg were comparable
Long-term studies			
Watts EST-2 1992	Menopausal symptom scale	Estratest® (33), Estratab® 1.25 mg (33)	Estratest®H.S. appears to be more effective in improving psychosomatic and psychological symptoms
Appel 030.8.01 1997	Menopausal symptom scale	Estratest® H.S. (81), Estratest® (73), Premarin® 0.625 mg (78), Premarin® 1.25 mg (79)	No consistent differences were seen between the effects of Estratest®H.S. and Premarin®0.625mg.

All seven of the studies used a menopausal symptom scale to assess potential relief of menopausal/vasomotor symptoms. Two of the studies included additional measures as well. Andrews study EST-1 and Bachmann study 030.0.13 each had three additional methods for assessing the patient's menopausal symptoms. Both also made use of a patient diary for recording number and severity of hot flashes, sleep habits, smoking, alcohol and caffeine consumption as well as time and dosing of medication each day. Bachmann study 030.0.13 also made use of the Greene Climacteric Scale for self-reporting of psychological and somatic symptoms, and a weekly rating scale for the patient self-evaluation of symptoms. Andrews study EST-1 made use of the Hopkins Symptom Checklist to measure anxiety, depression, obsessive-compulsive behavior, somatic symptoms and sensitivity, as well as incorporating the Total Beck Depression Inventory Score to evaluate psychological symptoms of patients. Lobo study S0303103 used the Menopausal Sexual Interest Questionnaire (MSIQ) and the Brief Index of Sexual Functioning in Women (BISF-W).

Five studies (Speroff EST-3, Raisz 030.0.12, Bachmann 030.0.13, Simon 030.0.0702, and Lobo S0303103) demonstrated significant effectiveness for Estratest® and all active treatment groups in improving menopausal/vasomotor symptom scores. In Raisz study 030.0.12, Estratest® provided significantly greater improvement compared to the two estrogen-only groups. An examination of somatic symptom relief between treatment groups at 3 weeks post-treatment showed the comparison of Estratest® vs. Estratab® had a p-value of 0.039. In addition, the Raisz study showed significant improvements for Estratest® vs. Estratab® in psychosomatic and psychological symptom measures as well. The Raisz study is the subject of a

Point-by-Point analysis of adequate and well-controlled clinical investigations included in this submission Volumes 3 and 11 through 16.

Although the Raisz study is referenced in the April 14, 2003 Notice in this proceeding, FDA only commented on the "potential positive effect [of androgens] on bone mineral density." 68 Fed. Reg at 17954. The statistically significant results with respect to the contribution of methyltestosterone to the relief of somatic, psychosomatic, and psychological symptoms associated with the menopause were not addressed by the Agency at all.

In Simon study 030.0.0702, Estratest® HS produced greater somatic symptom relief based on lower scores of a composite of hot flashes, sweats and vaginal dryness compared to 0.625 mg esterified estrogens. During the double-blind phase of this trial, in a visit-wise analysis of menopausal symptoms, the mean change from baseline was -0.79 for placebo, -1.79 for Estratest®, -2.93 for Estratest® HS, -2.53 for Estratab® 1.25 mg, and –1.20 for Estratab® 0.625 mg, with a between treatments p-value of 0.0102. In this study, the efficacy of Estratest® HS was equivalent to that of the higher dose of Estratab® at 1.25 mg, indicating that the addition of the androgen can result in equivalent relief with a lower dose of estrogen, an important advantage in light of the recent data from the Women's Health Initiative ("WHI"). The Simon study is the subject of a Point-by-Point analysis of adequate and well-controlled clinical investigations included in this submission in Volumes 3 and 4 through 9.

The Simon study was not referenced by FDA at all in the April 14, 2003 Federal Register Notice in this proceeding, despite the fact that it was published in the journal "Menopause" in 1999 and was also included by Solvay in its IND 41744.[31]

Sarrel study 030.0.10 was designed to examine efficacy of Estratest® in patients with inadequate responses to estrogen-only products (Estrace®, Estraderm®, or Premarin®). Although there were decreases from baseline seen in the Estratest® treatment group at weeks 4 and 8, none of the changes were statistically significant. Potential differences between groups were not discernible in this trial due to the small study size and short (8-week) treatment duration.

The results of the Speroff EST-3, Bachmann 030.0.13 and Lobo S0303103 studies each indicated that the Estratest® and Estratab® products provided relief from menopausal symptoms, but did not show differences between those treatments in the patient populations studied.

Because of inadequate patient recruitment, Andrews study EST-1 was judged by Solvay to be impossible to evaluate on its own, although it was possible to include the results from that study in the Meta-Analysis described below.

(d) Long Term Solvay Studies

The results of the two long-term studies conducted by Solvay with the Estratest® products are discussed here and also listed in Table 5. These studies were 24-month,

[31] The individual case report forms for the studies cited in this submission have not been submitted to the Solvay IND pursuant to 21 C.F.R. § 314.50(f)(2) and have not been included in this submission. Solvay will provide the individual case report forms upon request.

randomized, double-blind, and parallel group studies in bilateral oophorectomized - hysterectomized women.

Watts study EST-2 compared effects of Estratest® to Estratab® 1.25 mg, while Appel study 030.8.01 compared Estratest® and Estratest® HS to both the 1.25 mg and 0.625 mg strengths of conjugated equine estrogens (Premarin®) on bone mineral density. Both of these studies evaluated menopausal symptoms as a secondary objective.

A total of 377 surgically menopausal women were randomized to treatment between the two long-term studies conducted. Of those, 106 patients were randomized to Estratest® (both studies), 81 patients to Estratest® HS (one study only), and 190 patients to estrogen only groups (both studies). A total of 248 (65.8%) patients completed the trials out of the 377 patients randomized to treatment. Watts study EST-2 had a completion rate of 74.2%, and Appel study 030.8.01 had a completion rate of 65.8%. Both studies combined had a withdrawal rate of 34.2%.

Both long-term vasomotor studies for Estratest® measured and monitored menopausal symptoms, including somatic symptoms (hot flashes, sweats, and vaginal dryness), using a menopausal symptoms checklist at each office visit. Both studies showed similar results, with all active treatment groups producing a significant decrease in somatic symptom scores from baseline.

In Watts study EST-2, the Estratest® group had a statistically significant greater improvement than the Estratab® group in measures of psychosomatic symptoms at years 1, 1.5 and 2. Also, the difference between treatments as to overall psychological score was significant in favor of Estratest® at all time points except one month and year 2. With respect to the

measure of bone density, the Watts study showed a statistically significant difference between the Estratest® group and the Estratab® group with the Estratest® group having significantly greater positive change in bone mineral density. The Watts study is the subject of a Point-by-Point analysis of adequate and well-controlled clinical investigations included in this submission in Volumes 3 and 10.

Although the Watts study is referenced in the April 14, 2003 Notice in this proceeding, FDA only addressed the findings with respect to the observed incidence of hot flushes. As discussed, the incidence of hot flushes is only one of many relevant manifestations of menopausal or vasomotor symptoms. Moreover, the failure of the Watts study to demonstrate a statistically significant difference between Estratest® and Estratab® in that single parameter neither erases the significance of the other, positive findings of the study nor demonstrates that there is no such difference. The positive findings of the Watts study with respect to relief of psychosomatic and psychological symptoms associated with the menopause cannot be discounted and, indeed, as experts have concluded, fully support the prior and current DESI-effective indications for estrogen-androgen combinations. Certainly, the failure of the study to demonstrate a difference in the narrow category of hot flushes, when the study was neither designed nor powered to do so, does not establish a basis for changing the prior DESI-effective classification of these products.

(e) Solvay Study Meta-Analysis

In order to provide a combined overview of the results of the Solvay studies, Solvay has prepared an exploratory meta-analysis of the nine individual Solvay studies

investigating the effect of Estratest®, Estratest® HS, and Estratab® on menopausal symptoms.[32] This submission does not contain a Point-by-Point analysis demonstrating how Solvay's meta-analysis satisfies the criteria set forth in 21 C.F.R. § 314.126 because Section 314.200 of the Agency's regulations appears to envision submission of such point-by-point analyses only for individual studies. Nevertheless, FDA must consider the results of this meta-analysis in addition to the individual studies in determining whether Solvay is entitled to summary judgment or whether there are factual issues requiring a hearing in this matter. Since the promulgation of 21 C.F.R. §§ 314.200 and 314.126, meta-analyses have been increasingly relied upon by the scientific community and are now recognized as valid tools for evaluating quantitative evidence from two or more trials bearing on the same question. Indeed, FDA has recognized that meta-analyses may provide useful information regarding the efficacy of a drug product. See, e.g., *Guidance for Industry M4E: The CTD - Efficacy,* ICH (Aug. 2001); *Guidance for Industry E9 Statistical Principles for Clinical Trials*, ICH (Sept. 1998). Similarly, FDA has considered meta-analyses in connection with review of proposed health claims. See, e.g., 58 Fed.Reg. 2552 (Jan. 6, 1993) (Dietary Fiber and Cardiovascular Disease); 62 Fed.Reg. 3584 (Jan. 23, 1997) (Oats and Coronary Heart Disease); 64 Fed.Reg. 57700 (Oct. 26, 1999) (Soy Protein and Coronary Heart Disease).

Four Estratest® studies, Simon 030.0.0702, Sarrel 030.0.10, Raisz 030.0.12, and Bachmann 030.0.13, measured the subject's responses on menopausal symptoms using an instrument referred to as the Menopausal Rating Scale (MRS). The MRS consists of 10 menopausal symptoms which are grouped into 3 subscales: somatic, psychosomatic, and

[32] This meta-analysis was included as part of Solvay's "Summary of Estratest® Clinical Experience," which was submitted to IND 41744 on February 14, 2003.

psychological symptoms. Subjects' responses to each item were measured on a 4-point scale. The scores for each item were then summed to create the scores for the subscales as well as the overall score. Other Estratest® studies used different questionnaires to rate changes in menopausal symptoms. Because of the differences in the scales used in each of the studies, items were matched to the 10 items in the MRS. A summary of items matched to the menopausal symptom subscales is presented for the various studies in Table 6. The response ranges used in the meta-analysis are given for each study in Table 7.

Table 6. Items Matched to Menopausal Rating Scale Items Grouped by Study

Subscale	Symptom	Est-1/Est-2	Est-3	030.0.801	S0303103
Somatic	Hot Flashes	Hot flashes	Hot flashes	Hot Flashes	Hot Flushes or Flashes
	Sweating	Cold sweats	Cold sweats	Sweats	Night sweats; sweating
	Vaginal Dryness	Vaginal Dryness	Vaginal Dryness	Vaginal Dryness	Vaginal dryness during intercourse
Psychosomatic	Fatigability	Tired feelings	--	Tired feelings	Feeling tired or worn out; feeling a lack of energy
	Insomnia	Trouble sleeping	Trouble sleeping	Trouble sleeping	Difficulty sleeping
	Palpitations	Pounding of the heart	Pounding of the heart	--	--
Psychological	Irritability	Irritable and Nervous	--	Irritable and nervous	Being impatient with other people
	Nervousness	--	--	--	--
	Depression	Feeling depressed	--	Feeling depressed	Feeling depressed, down or blue
	Anxiety	Feeling tense or wound up; Worry needlessly; Attacks of panic	--	Feeling tense or wound up; Worry needlessly; Attacks of panic	Feeling anxious or nervous
	Lack of Concentration	Inability to concentrate; forgetfulness	--	Inability to concentrate; forgetfulness	Experiencing poor memory

Table 7. Response Ranges Used by the Menopausal Symptom Questionnaires Listed by Study

Studies	Range (Meaning)
030.0.0702, 030.0.10, 030.0.12, 030.0.13	0-3 (Absent, Mild, Moderate, Severe)
EST-1, EST-2	0-7 (Absent-0, Mild-1, Moderate-4, Severe-7)
EST-3	0-3 (Absent, Mild, Moderate, Severe)
030.8.01	0-7 (Absent-0; Mild-1,2,3; Moderate-4,5,6; Severe-7)
S0303103	0-6 (Not at all bothered – Extremely bothered)

In some cases, multiple items in a questionnaire would match to the item in the MRS. In this case, the average score of the matching items was used as the score for the MRS item. For some questionnaires, one item would match to multiple items on the MRS. In this case, the item score was used for only one item on the MRS (example: "irritable and nervous" was used for irritability on the MRS while nervousness was omitted).

The MRS used a 4-point response scale while many of the others questionnaires used wider ranges for their response scales. Percent change from baseline was used to standardize the scores.

The studies were grouped into short-term (6 months or less) and long-term (greater than 6 months). The short-term studies which had menopausal symptoms questionnaire information were: EST-1, EST-3, 030.0.0702, 030.0.10, 030.0.12, 030.0.13, and S0303103. The long-term studies were: EST-2 and 030.8.01. In addition, the Estratab® two-year study 008.00.02 was combined with the long-term Estratest® studies in order to provide information on the Estratab® 1.25 mg dose. The 008.00.02 study also used the Menopausal Rating Scale (MRS).

Percent change from baseline for the subscale and overall scores were analyzed using ANOVA with fixed factors treatment and center. Contrasts were used to compare Estratest® and

Estratest® HS with the corresponding doses of Estratab® and Premarin® or placebo. Statistical treatment group comparisons were performed at the 0.050 level of significance. Trends towards statistical significance were defined by p-values greater than 0.050 but less than or equal to 0.100. All subjects with post-baseline data were included in the analysis population; however, percent change from baseline could only be calculated for subjects with nonzero or non-missing baseline scores.

The results of the meta-analysis show the following:

- Improvement from baseline in somatic, psychosomatic, and overall subscales was generally significantly better with either an estrogen alone or Estratest® relative to placebo at most assessment points in both short- and long-term studies.
- The data are consistent with a dose response relationship with respect to Estratest® H.S. and Estratest® and Estratab® 0.625 mg and 1.25 mg in terms of change from baseline in subscales relative to placebo.
- **For all subscale scores at any assessment point in both short- and long-term studies, all significant between-treatment differences consistently favored Estratest® over Estratab®.**

The findings of the meta-analysis confirm that the addition of methyltestosterone to esterified estrogens, consistent with the DESI-effective indication for the combination, provides potential benefit to patients over and above that observed with estrogens alone in the treatment of menopausal symptoms. The meta-analysis also indicates that studies designed and conducted specifically to address this question as now raised by the Notice would similarly show a contribution of the androgen component to the overall effectiveness of the product that would be manifest in patients for whom adequate relief of symptoms is not achieved with estrogen supplementation alone.

iv. Study Data On Measures Of Bone Metabolism And Sexual Function Support The Contribution Of Androgen To The DESI-Effective Indications For Estrogen-Androgen Combinations

As discussed above, the constellation of symptoms associated with the menopause, whether termed "menopausal syndrome" or "vasomotor symptoms," involves various conditions which are inextricably interrelated to each other and to the hormonal changes associated with the menopause. For these reasons, studies of the effectiveness of hormonal therapy in measures of bone metabolism and sexual function/libido, changes in which are recognized to be associated with the menopause, need also to be considered in evaluating the effectiveness of therapy generally and the contribution of androgen to the effectiveness of combination estrogen-androgen therapy specifically. Additionally, insofar as the demonstrated effectiveness of estrogen-androgen therapy in these other measures provides additional bases for a physician to prescribe or a patient to prefer combination therapy when estrogen therapy alone is regarded as providing inadequate or unsatisfactory relief, these additional measures directly support the existing and prior DESI-effective indication for the combination. As Dr. Simon concludes in his declaration:

> Further, in my opinion, there is a segment of the menopausal population for whom combination estrogen/androgen therapy provides at least as safe and effective relief as estrogen alone but for whom the estrogen/androgen combination has potential added benefits of addressing ancillary menopausal symptoms without increasing the risks of therapy. Under these circumstances, in my opinion, the failure to consider these potential added benefits would not be in the best interest of the individual menopausal patient.

Simon Decl. at ¶ 13.

For instance, the effect of Estratest® on bone metabolism was assessed in the Watts study described above and in the accompanying Point-by-Point analyses. See Volumes 3 and 10. The Watts study EST-2 compared Estratest® to Estratab® 1.25 mg/d in a double-blind, randomized, 2-year, parallel-group study of 60 surgically menopausal women. The estrogen-androgen group showed significant increase from baseline in spinal bone mineral density at 12 and 24 months. In contrast, the estrogen-only group stopped bone resorption and showed an increase (P not significant) from baseline in spinal bone mineral density across that period of time. The difference in this parameter between the Estratest® and Estratab® groups was statistically significant.

Similarly, in a double-blind 2-year comparison, Barrett-Connor *et al*[33] studied the effects on bone mineral density, menopausal symptoms and lipid profiles of Estratest® and conjugated estrogens in surgically menopausal women. A total of 311 women were randomly assigned to one of four regimens: (1) conjugated equine estrogens, 0.625 mg/d; (2) conjugated equine estrogens, 1.25 mg/d; (3) Estratest® HS or (4) Estratest®. All treatments prevented loss of bone in the spine and hip. The full strength Estratest® regimen increased spine and hip bone mineral density more than other treatments ($p < .002$).

Davis *et al*[34] studied the long-term effects of estradiol and testosterone implants on bone mineral density and sexuality in a prospective, 2 year, single-blind randomized trial. Thirty-four postmenopausal volunteers were randomized to treatment with either estradiol implants 50 mg

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[33] Barrett-Connor E, Young R, Notelovitz M, *et al.* a two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. J Reprod Med 1999; 44:1012-20.

[34] Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995; 21:227-36.

alone or estradiol 50 mg plus testosterone 50 mg administered 3-monthly for 2 years. Cyclical oral progestins were taken by those women with an intact uterus. Bone mineral density of total body, lumbar vertebrae (L1-L4) and hip area increased significantly in both treatment groups, but increased more rapidly in the testosterone treated group at all sites. An analysis of the Davis study is included with this submission as part of the Point-by-Point analyses of adequate and well-controlled clinical investigations in Volume 3.

Aspects of sexual function, including sexual activity, satisfaction, orgasm, desire, and libido were examined in six randomized, controlled studies,[35,36,37,38,39,40] as described in Table 8. Consistently, in five of these trials, the addition of testosterone to a hormone therapy regimen was demonstrated to improve the specific aspects of sexual function to a greater degree than estrogen alone. This outcome was established using a number of tools, self-rating scales, diaries, interviews, and indices such as the Psychological General Well-Being Index, and the Brief Index of Sexual Functioning for Women.

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[35] Davis SR, McCloud P, Strauss BJ, Burger H. 1995.

[36] Burger H, Hailes J, Nelson J, Menelaus M. Effect of combined implants of oestradiol and testosterone on libido in post menopausal women. Br Med J (Clin Res Ed) 1987; 294:936-7.

[37] Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. Psychosom Med 1985; 47:339-51.

[38] Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. PG – 397-409. Psychosom Med 1987; 49.

[39] Shifren JL, Braunstein GD, Simon JA, *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000; 343-682-8.

[40] Laan E, van Lunsen RHW, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric 2001; 4:28-41.

As noted above, the Davis and Sherwin and Gelfand studies are also addressed in this submission as part of the Point-by-Point analyses of adequate and well-controlled clinical investigations in Volume 3.

In the study by Laan,[41] an androgen alone (not combined with estrogen) was associated with significant improvement in sexual function (desire, arousability, fantasies and lubrication) over placebo.

[41] Id.

Table 8. Controlled Clinical Studies in Sexual and Cognitive Function

Investigators	Study Design	Number Of Subjects / Drug Combinations	Dose Duration	Study Summary
Burger H, Hailes J, Nelson J, Menelaus M 1987	Randomized, single-blind	20 women oestradiol 40 mg implant oestradiol 40 mg plus testosterone 50 mg implant	Implant at 6 weeks, followed to 24 weeks	Loss of libido in the single implant group remained, combined group showed significant symptomatic relief (p<0.01). Increased libido, increased enjoyment of sex on self rating analogue scales.
Davis, S. R. McCloud, P. Strauss, B. J. Burger, H 1995	Prospective, single-blind, randomized	34 women enrolled 17 = estradiol 50 mg implants 16 = estradiol 50 mg plus testosterone 50 mg implants	2 years, administered tri-monthly	Combined therapy group experienced significant comparative improvement for sexual activity (P<0.03), pleasure (P<0.01), satisfaction (P<0.03), orgasm (P<0.035). Bone mineral density increased more rapidly in the testosterone treated group.
Sherwin, B. B. Gelfand, M. M. 1987	Double-blind, crossover	44 women estrogen 10 mg estrogen 8.5 mg plus testosterone 150 mg	1 month	Combined therapy group reported higher rates of sexual desire (p<0.01), sexual arousal (p<0.01), and numbers of fantasies (p<0.01) than E alone or placebo group. Changes covaried with plasma testosterone not with plasma estradiol levels. Rates of coitus and orgasm were also higher in the E-A group.
Shifren, J. L. *et al* 2000	Double-blind, crossover	75 women conjugated equine estrogens 0.625 mg, orally plus via transdermal patch: 150 mg testosterone or 300 mg testosterone or placebo	9 months total, patients received 12 weeks of each treatment (1 of the 3 possible transdermal patches plus estrogen).	Higher testosterone dose group had increased sexual activity scores for frequency of and pleasure-orgasm (P=0.03). The positive-well-being, depressed-mood, and composite scores of the Psychological General Well-Being Index also improved at the higher dose (P=0.04, P=0.03, and P=0.04, respectively, for the comparison with placebo).
Basaria, S. Nguyen, T. Rosenson, R. S. Dobs, A. S.[42]	Randomized, double-blind, parallel-group	40 women 1.25 mg oral esterified oestrogen 1.25 mg oral esterified oestrogen plus 2.5 mg oral methyltestosterone	16 weeks	A greater decrease in LH and SHBG levels in the combined therapy group (P = 0.01). Combined therapy group had higher free testosterone levels (P = 0.01), and significant decreases in plasma viscosity (P = 0.01), total cholesterol (P = 0.009), high density lipoprotein (HDL) (P < 0.001) and triglyceride (TG) levels (P = 0.001).
Regestein, Q. R. Friebely, J. Shifren, J. Schiff, I.[43]	Randomized, double-blind, active placebo-controlled, crossover	35 women 0.625 mg oral esterified estrogen 0.625 mg oral esterified estrogen plus 1.25 mg oral methyltestosterone	16 weeks	Combined hormone therapy significantly improved scores on a test of complex information processing, the Switching Attention Test (p<0.002).
Laan E, van Lunsen RHW, Everaerd W 2001	Randomized, double-blind, placebo-controlled	38 women tibolone 2.5mg/day or placebo	12 weeks	Vaginal pulse amplitude, sexual desire, frequency of arousability, sexual fantasies and vaginal lubrication were significantly increased compared to placebo.

[42] Basaria S, Nguyen T, Rosenson RS, Dobs AS. Effect of methyltestosterone administration on plasma viscosity in postmenopausal women. Clin Endocrinol (Oxf) 2002; 57:209-14.

[43] Regestein QR, Friebely J, Shifren J, Schiff I. Neuropsychological effects of methyltestosterone in women using menopausal hormone replacement. J Womens Health Gend Based Med 2001; 10:671-6.

Finally, in a 1988 study by Sherwin entitled "Affective changes with estrogen and androgen replacement therapy in surgically menopausal women," and published in the Journal of Affective Disorders, 14 (1988) 177-187, the combination of estrogen and androgen was found to contribute significantly to the reduction in dysphoric mood symptoms associated with the menopause. During weeks 1, 2, 3, and 4 of the study, women who received the estrogen-androgen combined drug reported less dysphoric mood than those in either estrogen-alone or untreated control groups ($p<0.01$) on the Daily Menstrual Rating Scale. This Sherwin study is the subject of a Point-by-Point analysis of adequate and well-controlled clinical investigations in Volume 3.

The critical relevance of these study findings is explained by the experts in the accompanying declarations:

> Indeed, while hormone therapy has not been shown to have a positive effect on mood or cognitive function not associated with vasomotor symptoms, effective treatment of the vasomotor symptoms of menopause may be critical to interrupting the quality-of-life sequelae of those symptoms, which certainly include effects on mood and cognitive function. In women experiencing this cascade of effects, it is generally unwelcome and unhelpful to suggest psychotherapy or SSRI therapy in lieu of effective treatment of the underlying menopausal syndrome. In approximately ten to twenty percent of menopausal women, these symptoms have a significant impact on their quality of life and their ability to function in today's highly competitive workplace. The significance of these issues to these women is often unappreciated by people who have not experienced them personally.

Young Decl. at ¶ 3.

> Further, in my opinion, there is a segment of the menopausal population for whom combination estrogen/androgen therapy provides at least as safe and effective relief as estrogen alone but for whom the estrogen/androgen combination has potential added

> benefits of addressing ancillary menopausal symptoms without increasing the risks of therapy. Under these circumstances, in my opinion, the failure to consider these potential added benefits would not be in the best interest of the individual menopausal patient.

Simon Decl. at ¶ 13.

Thus, the consistent results of these studies clearly indicate the advantages of using an estrogen-androgen combination, instead of an estrogen alone, with respect to bone loss, symptoms of sexual function and libido, and dysphoric mood often associated with the menopause. These advantages provide additional justification for the availability of the combination products as an alternative to estrogen-only therapy when estrogen-only therapy is found to provide inadequate or unsatisfactory relief.

v. The Pre-Eminent Experts In The Management Of The Menopausal Syndrome Have Concluded That Estrogen-Androgen Combination Products Are Essential Alternatives For Women Whose Symptoms Are Not Adequately Controlled By Estrogen Therapy Alone

Experts have uniformly and clearly expressed the view that the proper treatment of the menopausal patient requires therapy tailored to the individual.

> The safe and effective treatment of menopausal symptoms in the over forty million menopausal women in this country can be particularly challenging and requires tailoring therapy to the needs and responses of each individual patient.
>
> Estrogen and estrogen/progesterone therapies are the standard of care and typically constitute first line therapy, but such therapies do not always provide adequate relief. Further, attempts to achieve desired results by increasing estrogen doses and/or switching to other available estrogen dosage forms can ultimately be counterproductive. This is due to an increase in dose-dependent estrogen adverse reactions and an increase in sex hormone-binding globulin (SHBG) and a corresponding decline in bioavailable

> estradiol and androgen. Under such circumstances, combination estrogen/androgen products such as the Estratest® products typically are the only available alternatives for which there are sound scientific data and which clinical experience has repeatedly shown can provide adequate relief for a significant segment of the menopausal population.

Young Decl. and ¶¶ 3 and 5. See also Lobo Decl. at ¶ 4.

Moreover, the experts concur that the side effects of estrogen-androgen combination therapy are not significant impediments to their use in most cases.

> Because the levels of androgen in products such as Estratest® are low, side effects from the androgen are rare and there are no serious liver or lipid issues with the combination. Moreover, because the additional benefit from the androgen component is generally manifest quite quickly, the combination can easily be discontinued if the patient does not perceive an improvement in her symptoms.

Young Decl. at ¶ 6. See also Lobo Decl. at ¶ 4.

Finally, the removal of estrogen-androgen combination drug products from the market is regarded by the experts as a potential tragedy for the health and well-being of many, many women.

> In summary, it is my opinion, and the opinion of other qualified experts who have dedicated their professional careers to improving the quality of life of the ever-increasing number of menopausal women, that to remove the estrogen/androgen alternative would be a real tragedy and would effectively turn menopausal practice on its ear. There is no alternate means of providing such low doses of methyltestosterone. These products are supported by sound scientific data, including pharmacokinetic and pharmacodynamic studies and years of safe and effective clinical management of the menopausal symptoms. As our knowledge of and experience with these combination estrogen/androgen products has increased, it has become even more obvious that there exists a sound medical rationale supported by scientific data for using these products to relieve menopausal symptoms in women with a deficiency in

bioavailable androgen who are not obtaining adequate relief from estrogen therapy alone.

Young Decl. at ¶ 7.

I am not aware of any new data or information which would provide a scientific basis to question the appropriateness of the DESI "effective" classification. Indeed, the safe marketing history of the Estratest® products, my own extensive clinical experience, and our evolving knowledge of the chemical, physiological, biological, and pharmacokinetic effects of oral estrogen and androgen products, in my opinion, reinforce the appropriateness of the DESI "effective" classification for the Estratest® estrogen/androgen combination products.

In my opinion, if the Estratest® estrogen/androgen products were removed from the physician's armamentarium, a significant number of patients who were unable to obtain safe and effective relief from their vasomotor and associated symptoms prior to using the Estratest® products would be extremely unhappy. Physicians treating such patients would be obligated to turn to less regulated and more unpredictable alternatives in an attempt to relieve their patients' significant vasomotor and associated symptoms which in the absence of adequate relief, can, and do, have a significant impact upon a woman's quality of life.

Simon Decl. at ¶¶ 5 and 14. See also Lobo Decl. at ¶ 8.

In my opinion, if the Estratest® estrogen-androgen products were to be removed from the market, it would create chaos among the significant numbers of menopausal women for whom this combination has provided safe and effective relief and for whom standard available therapy failed. There simply is no currently available alternative therapy that can be used in lieu of the Estratest® products for this patient population who cannot obtain adequate relief of their vasomotor symptoms on medically accepted estrogen or estrogen-progesterone therapy alone. I therefore view it as imperative that the estrogen-androgen combination remain available to treat my patients.

Altman Decl. at ¶ 9. The attached declarations of pre-eminent experts in the management of the menopausal syndrome therefore make clear that the Estratest® products are essential alternatives for women whose symptoms are not adequately controlled by estrogen therapy alone.

e. There are No Available Alternatives to the Estratest® Products

The Estratest® products are the only estrogen-androgen combination products currently on the market. There is no currently available alternative therapy that can be used in lieu of the Estratest® products for the patient population who cannot obtain adequate relief of their vasomotor and associated symptoms on estrogen or estrogen-progesterone therapy alone. Altman Decl. at ¶ 9; Bachmann Decl. at ¶ 10; Declaration of Rogerio A. Lobo, MD ("Lobo Decl.") at ¶ 8; Simon Decl. at ¶ 14; Young Decl. at ¶ 7. If the Estratest® products were withdrawn from the market, it is likely that patients and physicians will seek to obtain less regulated and potentially more dangerous options including: (a) compounded estrogen-androgen combinations, which (assuming they can be secured) present quality control and variability concerns; (b) currently marketed single-entity androgen products intended for males which contain significantly higher levels of androgen and therefore are more likely to produce dose-dependent androgen-related side effects; and (c) dietary supplements, such as DHEA, which are extremely variable and unpredictable and have not been studied for long-term safety. Bachmann Decl. at ¶ 10; Lobo Decl. at ¶ 8; Simon Decl. at ¶ 14.

C. If a Determination Is Made that New Data are Necessary to Continue to Market the Estratest® Products, Solvay is Entitled to Additional Time to Generate Such Additional Data

If FDA concludes at this juncture that Solvay must generate and present new data in order to continue marketing the Estratest® products, Solvay is entitled to such additional time as

may be reasonably necessary to generate such data. Based upon the long-standing and current eligibility of the Estratest® products for ANDA approval, and the fact that DESI "effective" products are considered to be in compliance with the combination drug policy, there has been no regulatory need for Solvay to generate new clinical data with respect to the DESI effective indication.

As set forth above, the available data and marketing history establish that the Estratest® products are safe and effective for their recommended conditions of use. Indeed, in the absence of the proposed DESI amendment, the Estratest® products would be entitled to ANDA approval without the need to generate any new clinical data supporting FDA's current interpretation of "substantial evidence." As previously noted, Upjohn was able to obtain NDA approval of its Depo-Testadiol in 1980 without being required to generate any new clinical data (*i.e.*, clinical data satisfying 21 C.F.R. § 314.126 was either available in the public domain or subject to a waiver under 21 C.F.R. § 314.126(c)). Further, by not responding to Solvay's November 24, 1998 citizen petition, FDA has failed to support its erroneous determination that the DESI drugs were withdrawn for safety and effectiveness reasons insofar as the DESI drugs were offered for vasomotor symptoms. Therefore, under the currently effective DESI findings, the pending ANDAs for the Estratest® products are entitled to be approved.

Further, based on FDA's DESI effective determination for estrogen-androgen combination products, which creates a "statutory exemption or other form of permission" to file and obtain approval of an ANDA without needing to prove the safety and efficacy of the product for the DESI-effective indication, Solvay has a "license" under the terms of the Administration Procedure Act. See, e.g., 5 U.S.C. § 551(8); 57 Fed.Reg. at 17963. In order to withdraw or

revoke such a license, the licensee must be given both notice and an "opportunity to demonstrate or achieve compliance with all lawful requirements" prior to withdrawal or revocation of the license. 5 U.S.C. § 558(c). See also Atlantic Richfield Co. v. U.S., 774 F.2d 1193, 1200-01 (D.C. Cir. 1985) ("the licensee must be able to establish compliance with all legal requirements or must be able to change its conduct in a manner that will 'put its house in lawful order'") (quoting Blackwell College of Bus. v. Attorney Gen., 454 F.2d 928, 932 (D.C. Cir. 1972)).

Because there was no previous regulatory need for Solvay to generate any additional data to support the continued marketing of the Estratest® products, should FDA conclude at this time that additional data are necessary, Solvay is entitled to additional time to generate such data. Accordingly, the April 14, 2003 Federal Register proposal should be withdrawn or, at a minimum, modified to provide interested persons with a reasonable opportunity to generate and submit additional data to the docket affirming the appropriateness of the DESI "effective" classification.

D. Solvay Has Submitted To FDA A Detailed Plan For Generating Additional Data With Respect To The Labeled Indication As Well As The Widely-Used And Medically Accepted Off-Label Indication

Despite the fact that Solvay is not legally required to generate additional data to support the contribution of each component of the Estratest® products to the effectiveness of the Estratest® products, Solvay has nevertheless included as part of this submission additional data and expert opinions in support of the medical rationale of its combination estrogen-androgen products, including the contribution of each of their components. In addition, on March 27, 2003, Solvay submitted to FDA a detailed plan for generating additional data to further support both the labeled indication as well as the widely-used and medically accepted off-label

indication. See Estratest® and Estratest®HS Tablets General Investigational Plan (included in Volume 17 of this submission). Solvay is currently in the process of obtaining the Agency's comments on and concurrence with its investigational plans and protocols, having had a meeting with the Reproductive and Urologic Drugs Division of the Center for Drugs on June 9, 2003. Based on these ongoing discussions regarding the Agency's current data requirements and Solvay's commitment to carry out this study plan once it has received FDA's comments on and concurrence with it, Solvay submits that the results of these studies, once completed, must be considered in support of its request for hearing pursuant to 21 C.F.R. § 314.200(c)(2) and in support of Solvay's request herein that summary judgment be granted for Solvay.

E. Conclusion

FDA has failed to make a *prima facie* case to support the action proposed in its Notice. Further, FDA's conclusion stated in the Notice is incorrect: the evidence establishes that each component of Estratest® products contributes to the effectiveness of the products for their labeled indication and that the products are both safe and effective and generally recognized as safe and effective for their labeled indications. Accordingly, summary judgment must be entered in Solvay's favor. 21 C.F.R. § 314.200(g)(4).

V. AT THE VERY LEAST, SOLVAY IS ENTITLED TO A HEARING BECAUSE SUMMARY JUDGMENT IN THE FDA'S FAVOR IS PRECLUDED AS A MATTER OF LAW

If summary judgment is not entered in Solvay's favor, Solvay is nevertheless entitled to a hearing because, under applicable legal standards, summary judgment against Solvay may not be entered in light of the evidence presented.

A. The Agency Has Not Made A Showing Sufficient To Warrant Summary Judgment

1. FDA May Only Grant Itself Summary Judgment In Very Limited Circumstances

FDA's Notice uses the language of 21 C.F.R. § 314.200(g):

> A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing, together with a well-organized and full factual analysis of the clinical and other investigational data that the objector is prepared to prove in a hearing ... If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact to justify a hearing, or if a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

68 Fed.Reg. at 17956-57.

The historical development of this regulation demonstrates that the Agency's summary judgment procedure grew out of, and was adopted for use in, legal and factual situations quite different from those presented in this proceeding. Specifically, the 1962 Drug Amendments required FDA to reevaluate more than 4,000 outstanding NDAs that had been approved solely on safety grounds since the Act's passage in 1938. FDA was to withdraw approval of any NDA if the applicant did not come forward and satisfy a new standard — "substantial evidence" of the drug's effectiveness. "Substantial evidence" was defined by the 1962 legislation as "adequate and well-controlled investigations, including clinical investigations," and detailed regulations, adopted after notice and comment rulemaking, further particularized that definition. See 21 U.S.C. § 355(d); 21 C.F.R. § 314.126.

Because many of the drugs approved prior to 1962 lacked the data required to meet the new standard, the summary judgment procedure was chosen by the Agency as an alternative to holding thousands of unnecessary administrative hearings. In adopting the regulations now codified at 21 C.F.R. § 314.200(g), the Commissioner stated:

> [The regulations] are an adaptation of the summary judgment procedures of the U.S. District Courts; similar procedures are followed by a number of agencies called upon to cope with a very large docket of cases. These regulations are essential to the orderly and timely implementation of the NAS-NRC Drug Efficacy Review; without them the project could not be carried out within the foreseeable future.

35 Fed.Reg. 7250, 7251 (May 8, 1970).

Solvay acknowledges that agencies, like courts, may utilize summary judgment procedures where appropriate. See Federal Power Comm'n v. Texaco, Inc., 377 U.S. 33; reh'g denied, 377 U.S. 974 (1964); U.S. v. Storer Broad. Co., 351 U.S. 192 (1956). But the procedure is available only when it is clear that no issues of fact exist and, accordingly, the outcome of the controversy involved could not be affected by a hearing. USV Pharm. Corp., 466 F.2d at 460 n.5; Puerto Rico Aqueduct & Sewer Auth. v. EPA, 35 F.3d 600, 604-605 (1st Cir. 1994), cert. denied, 513 U.S. 1148 (1995). Agencies, including FDA, that utilize such procedures are bound in their application by the same standards of fairness as are the courts. See Hess & Clark, 495 F.2d at 984; USV Pharm. Corp., 466 F.2d at 461; Chicago, Milwaukee, St. Paul & Pac. R.R. Co. v. U.S., 585 F.2d 254, 260 (7th Cir. 1978). "The use of such [summary judgment] procedure puts a heavy burden on the agency to demonstrate that its procedure comported with fairness and requirements of the law." Citizens for Allegany County, Inc. v. Federal Power Comm'n, 414 F.2d 1125, 1128 (D.C. Cir. 1969).

2. To Sustain Summary Judgment In Its Favor, FDA Must Prove The Absence Of A Genuine Issue Of Material Fact

FDA, as the party seeking to amend the long-standing DESI finding of effectiveness for estrogen-androgen combination products, has the initial burden of proving that there exists new evidence or information that justifies a reversal of the Agency's and the NAS/NRC's previous findings of substantial evidence of effectiveness of these products for relief of vasomotor symptoms when estrogen alone does not provide adequate relief of these symptoms. As noted above, the Agency must first satisfy its initial burden of adducing evidence sufficient to warrant requiring the manufacturer to come forward with contrary evidence. Hess & Clark, 495 F.2d at 992. Only when FDA has satisfied this initial burden must the manufacturer come forward with contrary evidence. Id. See also USV Pharm. Corp., 466 F.2d at 461.

Moreover, because FDA has proposed summary judgment, it also has the burden of proving the absence of a genuine issue of material fact. Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986); Jeffery v. Sarasota White Sox, Inc., 64 F.3d 590, 593 (11th Cir. 1995). This burden is a heavy one. A court must reverse FDA's entry of summary judgment if it "harbors a doubt about any factual issue." E.R. Squibb, 483 F.2d at 1386. Summary judgment may be sustained only when the pleadings on their face "conclusively" show that a hearing can serve no useful purpose. Hess & Clark, 495 F.2d at 985. See also 21 C.F.R. § 314.200(g)(1). Where there is "any evidence which on its face" indicates a genuine and material issue of fact, a hearing must be provided. Hynson, 412 U.S. at 620.

If the evidentiary matter presented by FDA is insufficient to establish the absence of a genuine issue, summary judgment must be denied even if the opposing party presents no evidence at all. Adickes v. S.H. Kress & Co., 398 U.S. 144, 160 (1970). See also Morales v.

Am. Honda Motor Co., Inc., 71 F.3d 531, 534 (6th Cir. 1995) (non-moving party required to set forth specific facts only after moving party meets initial burden). Moreover, Solvay can successfully raise a genuine issue of fact precluding summary judgment merely by challenging the evidence adduced by FDA and raising substantial questions whether FDA has succeeded in carrying its initial burden of making a *prima facie* case. Hess & Clark, 495 F.2d at 992.

In determining whether genuine issues of fact exist, Solvay must be given the benefit of all reasonable doubts, and the evidence presented and inferences drawn must be construed in the light most favorable to Solvay. Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 587 (1986); U.S. v. Spicer, 57 F.3d 1152, 1159-60 (D.C. Cir. 1995), cert. denied, 516 U.S. 1043 (1996). The papers supporting the movant are closely scrutinized, whereas the opponent's are indulgently treated. Matsushita Elec. Indus. Co., 475 U.S. at 587; Adickes, 398 U.S. at 157. The dispositive issue at this stage is *not* whether the data are scientifically adequate, but whether on their face they are so conclusively deficient that the Agency could not accept them as adequate if it were so inclined. SmithKline Corp. v. FDA, 587 F.2d 1107, 1118-19, 1122, 1125 (D.C. Cir. 1978); 21 C.F.R. § 314.200(g).

As explained below, FDA has not made a *prima facie* case to support the proposed action in the Notice and therefore the Agency has not made a showing sufficient to support summary judgment in its favor.

B. On Its Face, Solvay's Evidence Is Sufficient To Preclude Summary Judgment For FDA

As discussed in considerable detail above, the relevant evidence in this proceeding, on its face, is overwhelmingly in Solvay's favor. Indeed, the evidence compels entry of summary judgment for Solvay and rescission of the Notice. At the very least, Solvay has presented

substantial scientific data and information that both: (1) raise substantial questions about the adequacy of FDA's purported showing that the Estratest® products fail to meet the standards of FDA's combination policy and (2) affirmatively demonstrate that the Estratest® products are safe and effective and generally recognized as safe and effective for their labeled indications and are in compliance with the combination policy. Thus, any material issues of fact cannot be disposed of by FDA's summary judgment procedures, but rather must be resolved through the hearing procedures.

In addition to scientific data and analyses, Solvay presents herein opinions from five leading experts who sharply disagree with FDA's allegations in the Notice and who conclude that FDA's actions are unwarranted based on the grounds cited in the Notice. See Altman, Bachmann, Lobo, Simon and Young Declarations. Where, as in this case, experts disagree with FDA's assertions concerning the challenged drug products and the proper interpretation of studies in the record, summary judgment for FDA cannot be sustained. American Cyanamid, 606 F.2d at 1323.

Even if these expert opinions are contradicted, the weight to be given to the opinions of Solvay's experts, as well as the weight to be given to the opinions of any opposing experts, can be measured adequately only at a hearing on the record, with full opportunity for cross-examination. When conflicting opinion evidence is presented, "then the case is simply not one to be determined on motion for summary judgment." Elliott v. Massachusetts Mut. Life Ins. Co., 388 F.2d 362, 365 (5th Cir. 1968). See also Thomas v. Newton Int'l Enters., 42 F.3d 1266, 1270 (9th Cir. 1994) ("Expert opinion evidence is itself sufficient to create a genuine issue of disputed fact sufficient to defeat a summary judgment motion"); Webster v. Offshore Food Servs. Inc.,

434 F.2d 1191 (5th Cir. 1970), cert. denied, 404 U.S. 823 (1971). The rationale behind this fundamental principle is that the weight to be accorded true opinion evidence is always for the jury or other trier of fact. Massachusetts Mut. Life, 388 F.2d at 365. See also Smith v. Hughes Aircraft Co., 22 F.3d 1432, 1441 (9th Cir. 1993); Eichelberg v. National R.R. Passenger Corp., 57 F.3d 1179, 1186 (2nd Cir. 1995) (credibility determinations are within the province of the jury and may not be resolved on a motion for summary judgment).

Similarly, if the evidence presented is subject to conflicting interpretations, or if reasonable persons might differ as to its significance, summary judgment must be denied. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 255 (1986); Mercantile Bank & Trust Co., Ltd. v. Fidelity and Deposit Co., 750 F.2d 838, 841 (11th Cir. 1985); Aketepe v. U.S., 925 F. Supp. 731, 733 (M.D. Fla. 1996), aff'd, 105 F.3d 1400 (11th Cir. 1997), cert. denied, 522 U.S. 1045 (1998). It is also firmly established that summary judgment may be improper even though the basic facts are undisputed if the parties disagree regarding the inferences to be drawn from those facts. Tao v. Freeh, 27 F.3d 635, 638 (D.C. Cir. 1994); Lighting Fixture and Elec. Supply Co. v. Continental Ins. Co., 420 F.2d 1211, 1213 (5th Cir. 1969).

Because this case turns in part upon the weight accorded to the expert opinions presented herein and upon the conclusions to be drawn from the studies presented, summary judgment is simply improper.

C. FDA May Not Grant Itself Summary Judgment On The Basis Of Its Fixed Combination Drug Policy

As noted above, it is clear that FDA is relying only on its fixed combination drug policy in proposing to amend the DESI finding of effectiveness for estrogen-androgen combination products. Indeed, FDA explicitly states in the Notice that it is relying solely on the combination

policy as the basis for amending the DESI effective classification of the Estratest® products: "for this indication there is not substantial evidence of the contribution of each component to the effectiveness of these combination drugs." 68 Fed.Reg. at 17953 (emphasis added). See also id. at 17955 ("FDA believes that substantial evidence is lacking that the addition of an androgen can improve the effectiveness of estrogen alone in the treatment of vasomotor symptoms (i.e., hot flushes)"). As set forth above, however, the Estratest® products comply with the combination policy in that they are subject to a DESI effective classification. 21 C.F.R. § 300.50(c). Further, data and information presented previously and herewith clearly establish that the Estratest® products meet all of the requirements of the combination policy. At a minimum, that data and information raises material issues of fact precluding summary judgment in this proceeding. Moreover, as shown below, FDA's fixed combination drug policy is not binding on Solvay and cannot properly constitute a basis for summary judgment.

1. The Combination Drug Policy Does Not Have The Force And Effect Of Law

In contrast to the regulations on adequate and well-controlled investigations set forth in 21 C.F.R. § 314.111(a)(5), summary judgment may not properly be based on a failure to comply with FDA's fixed combination drug policy.

As originally proposed, FDA's fixed combination drug policy was merely presented as a "statement amplifying" the requirement that an NDA "may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect." 36 Fed.Reg. 3126 (Feb. 18, 1971) (emphasis added). Moreover, the policy was described as a set of "criteria for rational combination drugs" for the "guidance of the regulated industry." Id. FDA continued to describe the policy as a "policy statement" and a "statement of general policy or

interpretation." 36 Fed.Reg. 20037 (Oct. 15, 1971). The combination policy was originally inserted in 21 C.F.R. Part 3, Subpart A (1973), which contained "Formal Statements of Policy or Interpretation." Although it was subsequently moved to Part 300 (21 C.F.R. § 300.50), its terms have not changed since 1971. FDA has thus never issued Section 300.50 as a substantive rule having the force and effect of law. Indeed, the Court of Appeals for the First Circuit has expressly noted that "the statement [of FDA's combination policy] purports to be no more than an indication of general policy." American Cyanamid Co. v. Richardson, 456 F.2d 509, 514 (1st Cir. 1971).

As a statement of general policy, Section 300.50 may indicate the approach that FDA will take in evaluating an NDA for a combination drug, but it is not legally binding on the public or on the courts. In particular, it is not legally binding on Solvay in this case and cannot even arguably support the amendment of the DESI finding of effectiveness for the estrogen-androgen combination products without the Agency presenting a *de novo* justification for the policy and a factual showing of the applicability of the policy to the facts and circumstances of this case. Thus, FDA's combination drug policy cannot form an adequate legal basis for denying the requested hearing.

2. The Combination Drug Policy Is Not Of The Type Approved By The Supreme Court As A Permissible Basis For Summary Judgment

Even assuming that FDA's combination policy is binding on Solvay, it cannot support a grant of summary judgment in favor of FDA. This is because the combination policy is not itself precise and cannot properly be read to invoke other requirements which may be regarded as precise. The Supreme Court in Hynson held that regulations establishing criteria for substantial "evidence consisting of adequate and well-controlled investigations" could support

administrative summary judgment because: (a) those regulations reduced the statutory standard to "detailed guidelines," Hynson, 412 U.S. at 618; (b) it was not disputed that the regulations "express well established principles of scientific investigation," id. at 618-19; and (c) as a result of the regulations, "drug manufacturers have full and precise notice of the evidence they must present to sustain their NDA's." Id. at 622. Indeed, the Court noted that FDA can determine "conclusively from the applicant's 'pleadings' that the application cannot succeed" only when the regulation in question is "precise." Id. at 621, 621 n.17. In the years since the Hynson decision, courts have consistently held that when the statute or regulation involved utilizes, but does not particularize, broad judgmental concepts, denial of a hearing is improper. See, e.g., American Cyanamid, 606 F.2d at 1312.

FDA may particularize applicable standards on a case-by-case basis, as an alternative to promulgating generally applicable regulations after notice and comment rulemaking. Id. at 1314. The Agency may not adopt this case-by-case approach, however, without providing notice to the applicant of the relevant standard. The Agency must then offer the applicant an opportunity to submit satisfactory evidence under the standard or to challenge the standard prior to the Agency's initiation of a summary judgment proceeding. Id. at 1312-14, 1323. Absent regulations adopted after notice and opportunity for comment, principles of fairness severely constrain FDA's authority to dispense with a hearing. Id. at 1323.

By its terms, a mere general statement of policy such as the combination policy in 21 C.F.R. § 300.50, which is vigorously disputed as a scientific principle and which lacks both precision and general acceptance, cannot provide the regulatory predicate for administrative summary judgment. Furthermore, the combination policy is not only itself inadequate under

Hynson to form the basis for summary judgment. It also cannot form the basis for extending FDA's definition of "adequate and well-controlled investigations" to showings of the therapeutic contributions of the individual active ingredients in a combination.

The standard under the Act for judging whether the DESI finding of effectiveness for estrogen-androgen combination products may be amended in this proceeding is whether "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have. . ." 21 U.S.C. § 355(e)(3). The "effect" of any drug is established by adequate and well-controlled investigations comparing the results of treatment with that drug with the results of administering a placebo or other appropriate control as provided in 21 C.F.R. § 314.111(a)(5)(ii)(a)(4). This "effect," in the case of the Estratest® products, is the effect of the drug product as an entity. The Act does not require any showing as to whether the effect of a drug is the result of particular active ingredients or whether each active ingredient necessarily contributes to that effect. Nothing in Section 505(e)(3) of the Act concerning substantial evidence of effectiveness requires or even suggests that a drug must be compared with another drug (here, with one of the individual active ingredients of the combination) for the purpose of showing that that drug is more effective than such other drug. Thus, to the extent that the Agency's combination policy requires such a comparison in order to show the contribution of each active ingredient of a combination, the policy impermissibly goes beyond the statutory requirements for proof of effectiveness under Section 505(e)(3) of the Act.

It is well-established that failure to prove relative efficacy (here, the increased effectiveness of a combination as compared to one of its components) is not a ground on which an NDA can be denied or revoked. The legislative history of the Drug Amendments Act of

1962, which added the "effectiveness" requirements to the new drug provisions of the Act, is replete with cautionary statements by members of Congress, as well as assurances by Government officials, that "...no such factor as relative efficacy appears." *"Drug Industry Antitrust Act." Hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary. U.S. Senate*, 87th Cong. 1st Sess. 2585 (1961). Senator Estes Kefauver, the primary sponsor of the bill, stated: "[L]et me make it quite clear that if we had meant to be talking about relative efficacy, we would have said so. We are talking about efficacy, not relative efficacy." Id. Similarly, the Secretary of Health, Education, and Welfare, Abraham Ribicoff, stated in testimony before the Senate Antitrust and Monopoly Subcommittee:

> Let me make it absolutely clear that we are not dealing here with what some have called "relative efficacy." The claim has been made before this Subcommittee that the proposed amendment would enable us "to decide the relative or comparative efficacy of a new drug in terms of drugs already on the market," or allow us to refuse clearance for a new drug merely because in the Food and Drug Administration's opinion, it is not the most efficacious drug for the purpose intended or is not as efficacious as one might ideally wish.
>
> The bill furnishes no basis for such apprehensions. The proposed amendments would merely require a showing that the new drug described in the application is safe for use and is effective for use, under conditions prescribed, recommended, or suggested in the labeling thereof. This would not require a showing of relatively greater efficacy than that of other drugs.

Id. (emphasis added). Accordingly, to demonstrate the effectiveness of the Estratest® products, Solvay cannot be required to prove that the Estratest® products are more effective than any other single or multiple-entity drug, including their individual constituents.

FDA may justify its combination policy on a safety basis: a concern for the exposure of patients to additional active ingredients in a drug product if no incremental benefit can be

expected from the additional ingredients. On this basis, however, there may still be no requirement that the contribution of each active ingredient in a combination be demonstrated by "substantial evidence" consisting of "adequate and well-controlled clinical investigations." Under the Act, evidence relating to safety is not subject to the substantial evidence test. E. R. Squibb, 483 F.2d at 1385; Edison Pharm. Co., 600 F.2d at 840-841. Rather, the statute requires "adequate tests" to show that a drug is safe for use under the conditions prescribed, recommended or suggested in the labeling thereof. 21 U.S.C. § 355(d)(1). Thus, assuming that the combination drug policy is valid at all, showings related to the contribution of each active ingredient of a drug product need involve only "adequate tests" and not "substantial evidence consisting of adequate and well-controlled investigations." Any data and information bearing on the justification for a combination may properly be considered in establishing the contribution of each active ingredient to the effectiveness of the drug. Such relevant data may include clinical experience, expert opinion, *in vitro* data, and other data which establish that the combination in question justifies the exposure of its users to more than one active ingredient.

FDA has, of course, not raised safety as an issue in this proceeding. Nevertheless, adequate data have been presented in this submission to establish compliance with the combination policy on this basis. See Section IV.B.2.d., above.

In any event, there is at the very least a material issue of fact as to whether the data and information submitted by Solvay are "adequate." Indeed, the Supreme Court in the Hynson case held that a standard which requires a determination the "adequacy" of certain data may not be a proper basis for administrative summary judgment under any circumstances. In discussing FDA's regulations defining "adequate and well controlled" clinical trials, the Hynson Court was

careful to indicate that summary judgment may be granted only in those cases where the regulatory provision allegedly violated is specific and does not allow for evaluative judgment:

> Some of the [FDA] regulations ... are not precise, as they call for the exercise of discretion or subjective judgment in determining whether a study is adequate and well-controlled. For example, § 130.12(a)(5)(ii)(*a*)(2)(*i*) requires that the plan or protocol for the study include a method of selection of the subjects that provide "*adequate* assurance that they are suitable for the purposes of the study."[44] The qualitative standards "adequate" and "suitable" do not lend themselves to clear-cut definition, and it may not be possible to tell from the face of a study whether the standards have been met. Thus, it might not be proper to deny a hearing on the grounds that the study did not comply with this regulation.

Hynson, 412 U.S. at 621 n.17 (emphasis in original). Because the standard of "adequate data" under the combination policy, even if it is properly applicable here, is similarly imprecise and qualitative, it cannot be relied on to justify the grant of summary judgment by the Agency to itself.

D. Conclusion

Each of the grounds asserted above is sufficient to preclude entry of summary judgment for FDA. They are not legal technicalities but, rather, go directly to the principal issues raised and to the character of the evidence presented. They constitute the essentials of due process and fundamental fairness. "Summary judgment is a lethal weapon and courts must be mindful of its aims and targets and beware of overkill in its use." Brunswick Corp. v. Vineberg, 370 F.2d 605, 612 (5th Cir. 1967). See also Liberty Lobby, 477 U.S. at 255 (trial court should act "with

[44] This regulation is now embodied at 21 C.F.R. § 314.126(b)(3), which states: "The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed."

caution" in granting summary judgment). As stated by Justice Cardozo in Ohio Bell Tel. Co. v. Public Utils. Comm'n of Ohio:

> Regulatory commissions have been invested with broad powers within the sphere of duty assigned to them by law. Even in quasi-judicial proceedings their informed and expert judgment exacts and receives a proper deference from courts when it has been reached with due submission to constitutional restraints. Indeed, much that they do within the realm of administrative discretion is exempt from supervision if those restraints have been obeyed. All the more insistent is the need, when power has been bestowed so freely, that the "inexorable safeguard" of a fair and open hearing be maintained in its integrity. The right to such a hearing is one of "the rudiments of fair play" assured to every litigant by the Fourteenth Amendment as a minimal requirement. There can be no compromise on the footing of convenience or expediency, or because of a natural desire to be rid of harassing delay, when that minimal requirement has been neglected or ignored.

301 U.S. 292, 304-305 (1937) (citations omitted).

This is not a case where the respondent's data on their face fail to meet statutory criteria, as particularized by regulations. Rather, it is a case where the standards that Solvay has allegedly failed to meet have not been articulated, explained, or justified. Especially in light of the long-standing basic principles applicable to summary judgment proceedings, FDA has not demonstrated the absence of material issues of fact, while Solvay has clearly shown that, at a minimum, many such issues exist. Thus, unless FDA's Notice is rescinded, the only fair and legally permissible alternative in this proceeding is that the hearing request be granted.

VI. EVEN IF SUMMARY JUDGMENT AGAINST SOLVAY IS CONSIDERED, IT MAY NOT BE ENTERED UNTIL SOLVAY HAS BEEN SERVED WITH A PROPOSED ORDER

A. The Federal Register Notice Is A "General Notice"

Under the Agency's regulations, a notice of opportunity for a hearing may be either "general" or "specific." 21 C.F.R. § 314.200(a)(1). To be "specific," a notice must either refer to specific requirements in the statute and regulations with which there is a lack of compliance or provide a detailed description and analysis of the specific facts relied upon by the Agency. If the notice summarizes in a general way the information relied upon, it is deemed "general." Id.

Although the Notice in this proceeding purports to be "specific" in that FDA lists data and information it relies on as the basis for its conclusion that there is a lack of substantial evidence that estrogen-androgen products comport with the Agency's combination drug policy, it is in fact "general" within the meaning of the regulation. See 21 C.F.R. § 314.200(a)(1). FDA's Notice does not provide a detailed description or analysis of all the currently available scientific data in support of the safety, effectiveness, and medical rationale of the Estratest® estrogen-androgen combination products or why these data and expert opinions relating to such data individually and collectively do not provide adequate factual, scientific, and legal bases in support of retaining the DESI "effective" classification and correspondingly approving the pending ANDAs.

It is well settled that an applicant is denied the required notice of the Agency's grounds for withdrawal when the ultimate basis for withdrawal is not the same as that stated in the notice. See, e.g., Sterling Drug, Inc. v. Weinberger, 503 F.2d 675, 681-82 (2nd Cir. 1974). As the court explained:

> The petitioners were not required to indulge in such guesswork. They were entitled to a notice of the specific grounds on which the FDA proposed to withdraw approval of the [] NDA's and to an opportunity to submit evidence which would entitle them to a hearing before an order of withdrawal could be validly issued.

Id. at 682.

In the instant case, FDA's Notice merely lists references and states conclusorily that there is a "lack of substantial evidence" of the contribution of each component to the effectiveness of these combination drugs." 68 Fed.Reg. at 17953. Further, the Notice fails to list or address at all some of the studies upon which Solvay relies. Accordingly, this case presents even more compelling facts to warrant a hearing than those in Sterling Drug. Because FDA has not yet provided the detailed analysis required, and no analysis at all of some of the studies on which Solvay relies, Solvay cannot anticipate and answer at this stage of the proceeding any questions or criticisms which FDA might raise regarding the studies or the other data and information presented in this submission. Under these circumstances, summary judgment cannot be entered until Solvay is provided an opportunity to review and respond to FDA's evaluation of all of the studies and other arguments submitted herein. See SmithKline Corp., 587 F.2d at 1125-26 (remanding to FDA for further proceedings, primarily because the petitioner did not have an adequate opportunity to review and respond to FDA's evaluation of the petitioner's proffered data).

The applicable regulations provide that when FDA issues a general notice, as it did here, summary judgment may not be entered until the party requesting a hearing has an opportunity to respond to FDA's specific criticisms of the data presented. 21 C.F.R. § 314.200(g)(2). Specifically, if FDA concludes that summary judgment against Solvay should be considered,

FDA must serve upon Solvay a proposed order denying a hearing and allow Solvay sixty days to respond with sufficient data, information, and analyses demonstrating that there is a genuine and substantial issue of fact justifying a hearing. Id.

Solvay has presented evidence demonstrating that the Estratest® products are both safe and effective and generally recognized as safe and effective for their labeled indication. Therefore, summary judgment against Solvay need not be further considered. If, however, FDA disagrees, Section 314.200(g)(2) of the Agency's regulations unequivocally requires that a proposed order be served prior to the issuance of a final order.

B. Even If the Notice Is "Specific," A Proposed Order Must Be Issued Prior to Issuance of a Final Order

Even if the April 14, 2003 Notice is deemed to be a "specific" notice, FDA is still obligated to issue a proposed order before summary judgment against Solvay may be entered. The relevant case law and FDA's own regulations require that when a request for a hearing is supported by data, information, and expert opinion which has not previously been reviewed by FDA, such as that provided in this submission, the manufacturer must be given notice and an opportunity to respond to FDA's criticisms of the data, articulated in the form of a proposed order, prior to the summary denial of a hearing request. See 21 C.F.R. § 314.200(g)(3). Because Solvay has presented data, information, and expert opinion which has not previously been considered by FDA, such a proposed order is required in this case.

Even before promulgation of 21 C.F.R. § 314.200(g), the U.S. Court of Appeals for the D.C. Circuit addressed the requirement that, prior to the issuance of a final order, a drug manufacturer be given adequate notice and an opportunity to respond fully to the specific

allegations on which FDA relies to conclude that there are no material issues of fact requiring a hearing. In Hess & Clark, the court explained this principle as follows:

> agencies are governed by . . . basic requirements of fairness and notice, and these include specificity of notice and opportunity to respond if what is instituted is intended to be a procedure for summary disposition without hearing. If the Commissioner of FDA is relying on his Notice as a device for invoking a summary judgment procedure that avoids the statute's general requirement of a hearing, he must include in such notice references to the "facts" that he deems to be established in order that there may be meaningful opportunity to controvert the alleged facts and present a material issue for hearing. This includes, at a minimum, presentation of the *prima facie* case required in USV as a predicate for withholding the hearing required in general for revocation of an approved application.

495 F.2d at 984.

In specific response to the Hess & Clark decision, in 1974 FDA adopted procedural regulations that were intended to ensure that adverse parties receive adequate notice and an opportunity to respond to FDA's criticisms of the studies relied on by the parties. See 39 Fed. Reg. 9750 (March 13, 1974). Those regulations provide:

> When following a general or specific notice of opportunity for hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the [Center] concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

21 C.F.R. § 314.200(g)(3).

As discussed above, there are no particularized regulations defining the type of data required to comply with the combination policy. Nevertheless, Solvay has submitted data and

information directly contradicting FDA's assertions, including reports of adequate and well-controlled clinical investigations and expert opinions that were not reviewed or cited by FDA in the Notice. Under such circumstances, FDA is, at a minimum, required to issue a proposed summary judgment order prior to denying Solvay's request for a hearing. 21 C.F.R. § 314.200(g)(3).

In short, the evidence establishes that the Estratest® products are safe and effective and generally recognized as safe and effective for their labeled indications and comply with the Agency's combination drug policy. If, however, FDA disagrees, Sections 314.200(g)(2) and (3) of the Agency's regulations require that at the very least a proposed order be served prior to the issuance of a final order.

C. If Solvay's Evidence Is Found To Be Insufficient, Solvay Must Be Given An Opportunity To Produce Adequate Evidence Prior To Any Entry Of Summary Judgment In FDA's Favor

As emphasized throughout this submission, Solvay believes that the evidence conclusively demonstrates that the Estratest® products are safe and effective for their labeled indication and thus that summary judgment must be entered in Solvay's favor. Indeed, because FDA's Notice is insufficient and unsupported by the evidence cited therein, this conclusion would be compelled even if Solvay had submitted no evidence whatsoever.

Nevertheless, should FDA determine that that the data generated to date and submitted herein are inadequate and that additional data from Solvay are necessary to resolve the issues presented, Solvay must be given notice of the alleged deficiencies and additional time in which to generate and submit the additional data requested by FDA. This opportunity is necessary because FDA has not promulgated generally applicable regulations which identify the type of

data a manufacturer must submit in order to meet the combination policy requirements and because, prior to publication of the Notice, the Agency had not taken the position that additional data needed to be generated to preserve the long-standing DESI-effective status of estrogen-androgen combination drug products.

As the D.C. Circuit explained in a case raising the issue of a drug's safety, which, like the combination policy, is not a concept that has been particularized by Agency regulations:

> When, however, FDA proceeds by way of ad hoc articulation of safety standards, it is clearly incumbent upon it to give the applicant notice of those standards and of the manner in which the data before it failed to meet them. This notice must be given in timely fashion to put the applicant in position to dispute FDA's interpretation of the Act's safety criteria, object to FDA's critique of the submitted studies, and conduct and proffer new studies meeting the newly-articulated requirements. Should the applicant then identify a material issue of fact, FDA must hold a hearing.

American Cyanamid, 606 F.2d at 1314 (citation omitted). See also Marshall Minerals, Inc. v. FDA, 661 F.2d 409, 418 (5th Cir. 1981), reh'g denied, 671 F.2d 1379 (5th Cir. 1982).

The court explained that the only exception to this rule would be a situation in which FDA's rejection of data under the broadly defined statutory standard was "unimpeachable" and "unassailable," as would be the case where, for example, 50 percent of the subjects in a safety study died from the recommended dosage and regimen of the drug. American Cyanamid, 606 F.2d at 1314. In the absence of such extreme facts, summary judgment in favor of FDA may be sustained only if the respondent "has been afforded time to present compliant tests" under a particularized applicable standard. Id. at 1315. See also 5 U.S.C. § 558(c); Atlantic Richfield, 774 F.2d at 1200-01.

In this case, as discussed above, the Agency has not promulgated any regulations specifying the combination policy requirements. Therefore, if after its review of this submission FDA determines that Solvay's data are insufficient, the Agency must first give notice of the standard it believes to be applicable, and then provide Solvay both with an opportunity to question that standard and adequate time to conduct and offer studies which meet the articulated criteria.

VII. OBJECTIONS TO REQUIRED FORMAT

This submission complies with the requirements of 21 C.F.R. § 314.200(d) by providing data, including studies where pertinent, information, and expert opinions setting forth the scientific basis for the conclusion that the Estratest® products comply with the Agency's combination drug policy. Solvay objects, however, to FDA's purported requirement that an applicant for a hearing be required to argue and prove its entire case in detail as a prerequisite to the Agency's consideration of whether a hearing is justified by any legal principle. This purported requirement is particularly inappropriate in a proceeding such as this, where it is FDA, not Solvay, which is proposing to amend the existing and long-standing DESI "effective" classification and thus has the burden of establishing the reasonableness of the proposed amendment (*i.e.*, the existence of new information which justifies the rescission of the Agency's and NAS/NRC's finding of "effectiveness" of the Estratest® estrogen-androgen combination products for their labeled indications). It is the nature and quality of FDA's evidence, not Solvay's, which is at issue at this stage of the proceeding.

Moreover, the requirement for the submission of raw data set forth in 21 C.F.R. § 314.200(d) (which, it is assumed, refers to the individual case records) is a clearly unreasonable

burden when required as part of an initial request for a hearing. This is demonstrated by FDA's regulation at 21 C.F.R. § 314.50(f)(2) which states that submission of such data is not ordinarily required. While the raw data may be useful at a hearing to examine the validity of an investigator's conclusions, such data should not be considered necessary to establish whether the results of the study present a *prima facie* case in support of a hearing. There may even be studies for which the raw data are no longer available. Yet these studies may be relevant evidence and should be considered.

The heavy burden imposed by the regulation is further magnified by the fact that this entire submission was required to be completed and submitted within 60 days. An administrative agency has considerable discretion in promulgating procedural regulations, but such discretion is not unlimited. As stated by the Supreme Court, "FDA does not have unbridled discretion to do what it pleases. Its procedures must satisfy the rudiments of fair play." Hynson, 412 U.S. at 627.

The Act does not authorize FDA to take action against a drug under Section 505 because of the failure to submit data, or a request for a hearing, in conformity with a particular format. It is the substance of the data, and the safety and effectiveness of the drug, that should be controlling.

VIII. VERIFICATION

I am the person responsible for the preparation and compilation of this submission, in consultation with Solvay's medical and scientific staff, outside medical investigators and consultants, and private regulatory counsel.

I have made every reasonable effort to ensure the inclusion of all information required to be contained (or incorporated by reference) in the submission under 21 C.F.R. § 314.200(d). To the best of my knowledge and belief, relying in part upon my assistants and advisors, this submission is in full compliance with those requirements.

Walt Addison Linscott, Esq.
Vice President Law, Government and Public Affairs
Solvay Pharmaceuticals, Inc.

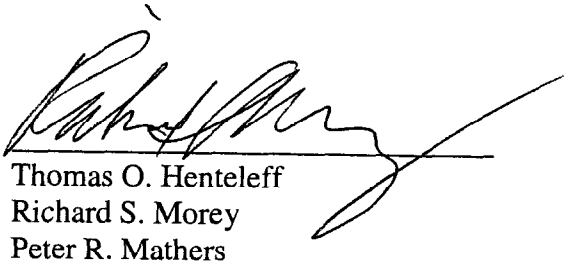
Date June 12, 2003

IX. CONCLUSION

As demonstrated above, there is no "new information" demonstrating a lack of substantial evidence that the Estratest® products are effective for their labeled indications. On the contrary, Solvay has established that the Estratest® products are both safe and effective and generally recognized as safe and effective for their labeled indications. Solvay therefore requests that the Commissioner enter summary judgment in favor of Solvay and rescind the notice of opportunity for a hearing in accordance with 21 C.F.R. § 314.200(g)(4). In the alternative, Solvay requests that the Commissioner set a hearing for the trial of any unresolved factual or policy issues presented by this request for a hearing and any supplemental submissions thereto in accordance with 21 C.F.R. § 314.200(g)(5) and declare, in accordance with 21 C.F.R. § 314.200(g)(6), that a hearing of the issues in this case is in the public interest. If summary judgment against Solvay is nevertheless considered, Solvay requests that the Commissioner

direct the Agency to serve a proposed order in accordance with 21 C.F.R. §§ 314.200(g)(2) or (g)(3).

Respectfully submitted,



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