DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 11 2000

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Dr. Sherman Frankel
Department of Physics
University of Pennsylvania
290 South 33rd Street,
Philadelphia, PA 19103

Re: Docket No. 00P-1330/CP1

Dear Dr. Frankel:

This letter responds to your petition dated May 30, 2000, asking the Food and Drug Administration to reconsider its approval of the drug Propecia and to amend or revoke a regulation approving it. For the reasons that follow, the petition is granted in part and denied in part.

Propecia (finasteride 1 milligram (mg)) is approved for the treatment of male pattern hair loss. It works by inhibiting an enzyme that converts testosterone to dihydrotestosterone (DHT). You claim that 1 mg is a higher dose than is needed for effective treatment with Propecia. The basis for your claim is that you interpret data submitted to the Propecia NDA as showing that "the reduction in conversion of testosterone to dihydrotestosterone set in at .05 mg . . . ." (Petition at 1). The meaning of this statement is clarified by your article entitled "Study of the Food and Drug Administration Files on Propecia," published in the March 1999 issue of the *Archives of Dermatology*. In the article, you discuss a pharmacodynamic study that compared various doses of Propecia. Samples were taken from the scalps of subjects and the amount of dihydrotestosterone (DHT) in the sample was measured. You state that the percent change in DHT "dropped to 60% for a 0.05-mg dose and stayed that way for all doses up to 5 mg. Thus, a 20 times smaller dose than that recommended had the same effect on DHT" (p. 257).

Your conclusion that conversion of DHT plateaued at the .05 mg dose is not entirely accurate. The data show the mean scalp DHT reduction was -55.90 at the .05 mg dose, -53.95 at the .2 mg dose, -57.56 mg at the 1 mg dose, and -65.24 at the 5 mg dose. These data suggest a possibility of further drug effect beyond 1 mg. Even if your interpretation of the data were correct, however, it would have been inappropriate for FDA to rely on the pharmacodynamic study discussed above as primary evidence for the proper dose of Propecia because there is no established correlation between a reduction in the amount of DHT measured from a scalp sample and the amount of hair grown.

You state that a key question is whether efficacy should be measured by testosterone conversion or by "subjective questionnaires on efficacy" (Petition at 2). This statement appears to reflect your opinion that testosterone conversion is a better measure of effectiveness than subject questionnaires and implies that results from subject questionnaires were the only endpoint FDA examined to assess the effectiveness of Propecia. In fact, FDA assessed the effectiveness of Propecia in clinical studies that included four measures of effectiveness: counting hairs, subject

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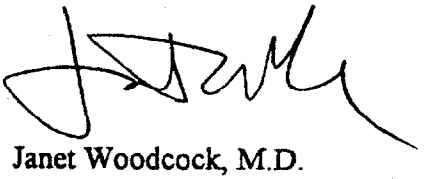
questionnaires, global assessment by the investigator, and photographic evaluation by a panel of dermatologists. All four of these clinical endpoints demonstrated effectiveness. Furthermore, as discussed above, reduction in the amount of DHT as measured from a scalp sample is not a validated endpoint.

You also state that the efficacy data upon which approval was based lacked the "statistical accuracy to prefer 1 mg over .2 mgs and no studies were shown down to .05 mg" (Petition at 1). You claim that clinical trials should have studied Propecia at low dosages because Propecia must be taken throughout the patient's lifetime to ensure continued and retained hair growth. You conclude that Propecia should not be approved at the 1 mg dosage until "data are provided to the FDA showing efficacy studies at the lower dosages of sufficient statistical accuracy and with clear presentations of the effects of systematic errors in the studies" (Petition at 1).

We interpret your statement "[t]hat the efficacy data submitted to FDA did not possess the statistical accuracy to prefer 1 mg over .2 mgs. . . ." (Petition at 1) to mean that there was not a statistically significant difference between these doses. FDA does not require that a dose-ranging study demonstrate statistical significance between doses; showing a positive slope in the dose-response curve, as did the Propecia study, is sufficient. You also object that there were no studies "down to .05 mg" (Petition at 1). It is true that the dose-ranging study did not include a .05 mg dose. It did, however, include an even lower dose, .01 mg, in addition to .2 mg and 1 mg doses. The study showed the .01 mg dose to be ineffective, and the 1 mg dose to be more effective than the .2 mg dose and equally safe.

In conclusion, your request is granted in part in that FDA has reconsidered the studies upon which approval of Propecia was based. Although you did not specifically request that FDA withdraw approval of Propecia 1 mg, the Agency concludes that, on the basis of all the evidence available to the Agency, including the information in your petition, there are no grounds for withdrawal of approval under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(e)). Your request that the Agency amend or revoke a regulation approving Propecia is denied because there is no regulation concerning Propecia.

Sincerely yours,



Janet Woodcock, M.D.
Director
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