APPENDIX XV

U.S. GOVERNMENT MEMORANDUM

MAY 11, 1960.

To: Geo. P. Larrick, Commissioner of Food and Drugs.
From: Bureau of Medicine.
Subject: Enovid Tablets—NDA 10-976.

The New Drug Branch has concluded that the evidence establishes the safety of Enovid Tablets for oral use in conception control and has issued a letter on April 22, 1960, making conditionally effective a supplemental application for this purpose. Because of the considerable general interest and possible objections from some quarters with respect to our action in clearing the drug for such use, we are furnishing the following information concerning the basis for our action.

On the basis of the original data and the presently submitted data G. D. Searle and Company have recommended that Enovid be used for contraceptive purposes at a dose level of one 10-milligram tablet daily starting from day 5 to day 25 of menstrual cycle. Because the studies did not progress beyond 3 years and in view of the lack of longer clinical experience, Enovid is proposed to be limited for use for this purpose to 2 years. This product has always been limited to prescription sale and will continue to be dispensed on prescription.

A supplement for this New Drug Application was conditionally filed on October 29, 1959. This supplement proposed the use of Enovid Tablets for conception control. The original New Drug Application was made conditionally effective May 21, 1957, and fully effective June 10, 1957. Enovid has been on the market since that time. However, it was made effective for its progestational activity and has not been labeled for conception control although we knew at the time of original submission that it does inhibit ovulation. The initially indicated progestational uses of this product were amenorrhea, primary or secondary, Metrorrhagia, menorrhagia, habitual abortion, the inadequate luteal phase as a potential cause of infertility, threatened abortion, idiopathic infertility, endometriosis, premenstrual tension, and dysmenorrhea. Because of the short-term nature of the indications it has not been used for more than 3 or 4 months at a time except in endometriosis in which condition it has been used for periods up to 10 months.

The following studies were conducted in support of this supplemental application proposing the use of Enovid for conception control.

In the initial and subsequent studies it was shown that Enovid does, in fact, prevent ovulation. In April 1956, the first study to investigate the practical usefulness of this agent to control population increases was undertaken. At present, there are 2 studies in Puerto Rico; 1 in Port-Au-Prince, Haiti, and 1 in Rio Piedras section of San Juan, Puerto Rico. The following points were and are being studied:

(1) Inhibition of ovulation over long-term cyclic administration.

On medication 2.7 pregnancies per 100 woman-years occurred. Gregory Pincus, M.D., Shrewsbury, Mass., states that the pregnancies that occurred were due to irregular tablet taking. Edward Tyler, M.D., University of California Medical School, reports 8.6 percent pregnancies (22 pregnancies in 3,082 woman-months), but some of these patients were on other progestational agents such as 17-alpha-acetoxy progesterone and 9-alpha-11-ketoprogesterone. Normally, the pregancy rate in normal woman in the reproductive phase of life under conditions of regular exposure is in the range of 75–85 per 100 women-years. Incidentally, the contraceptive efficacy of other devices under normal conditions of use ranges from 2–10 percent. Therefore, it can be assumed that the product on daily use in efficacious for this indication and if properly used better than the usual mechanical means.

(2) Effect on the menstrual cycle.