DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
May 28, 1968.

Attention Fred M. Vinson, Jr., Assistant Attorney General.
Re Syntex Laboratories, Inc. Your ref: FMV:JWK:mch 21-48-353, FDC No. 53222.

Hon. RAMSEY CLARK,
Attorney General,
Department of Justice,
Washington, D.C.

DEAR SIR: This is with reference to your letter of April 22, 1968, and the United States Attorney's letter of May 21, 1968, declining prosecution on both the advertising and the labeling violations we have reported to you.

The United States Attorney declines for the reasons that (1) there is a reasonable doubt whether the labeling (FDA monograph) is substantially different from the approved labeling, (2) the violations appear to be the result of honest differences of opinion as to what is required, and (3) the offense is almost three years old and ther eare no indications of violations since 1965.

(1) There can be no reasonable doubt that the PDR differed from the approved labeling in a substantial way. It was too brief, it was promotionally slanted, and it omitted important information for safe prescribing.

(a) A comparison of the approved labeling and the PDR monograph plainly shows that some of the most vital safety information was omitted from the monography. A copy of the 1965 omnograph is enclosed. It exaggerates the effectiveness of the drug, and it minimizes the side effects, precautions and contraindications. We simply cannot understand how it can be said that this abbreviated material, and particularly the seven lines devoted to side effects, can possibly be said to be substantially the same as the approved directions for safe use of this drug. The substance of the monograph and the substance of the approved labeling are not the same.

Fundamentally, what the Company did was to present a reassuring write-up for the physician's desk which omitted the most important information he needed to have to prescribe this drug for his patients with safety. As the criminal information which your office drafted shows, the physician was not alerted to the possibility of effects on the fetus if a pregnant woman should take the drug not knowing she was pregnant, he was not alerted to the limited experience with the drug and its possible long range effects upon a variety of organ and endocrine systems, including pituitary, ovarian, adrenal, uterine, liver, and thyroid, he was not alerted to the possibility of intravascular clotting (a risk now known to be even more serious than in 1965), he was not warned about effects on patients with any condition involving calcium or phosphorus metabolism, and he was not told to use the drug with care in any patient who had a history of psychic depression.

We feel confident that we can prove by acceptable medical evidence that the prescribing information in PDR-1965 was *not* substantially the same as the approved labeling, as the regulations require. And we are equally confident that we can prove the omissions and changes were significant from the standpoint of patient safety. Our Advisory Committee on Obstetrics and Gynecology, quoted in the Company's labeling, said that the physician must decide for his patient whether to accept the risk involved in the use of oral contraceptives, small though it may be, but that he "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data." The PDR monograph did not serve this purpose, and the violative ads we will discuss later compounded the hazard.

(2) There was no basis for considering this violation a result of an honest difference of opinion as to what is required. The applicable regulations had been in effect since 1961, and the Company's performance shows that it did not comply with what was clearly required—it did not present substantially the same information in PDR as in the approved labeling. It had the labeling at hand and it chose to omit some of the information from the PDR monograph.

(3) Syntex has not been in compliance since 1965. The ad charges you eliminated would have shown the United States Attorney that the same failures to inform continued after that date. And within the past few months, on January 22, 1968, we required the Company to mail a letter to all physicians in the United States calling attention to its failure to include in its then current ads appropriate warnings about use of the drug in psychic depression and about the possibility of thromboembolic episodes. A copy of the letter is enclosed.