MEMORANDUM

JULY 8, 1964.

To: Joseph F. Sadusk, Jr., M.D., Medical Director, Bureau of Medicine.
Through: Ralph G. Smith, M.D., Director/DND.
From: Mathew J. Ellenhorn, M.D., Chief, New Drug Surveillance Branch.
Subject: NDA 12-462 Lomotil safety and efficacy. Recommendations for action on new drug application.

(G. D. Searle & Co., Chicago, Ill., AF 13-505)

I have reviewed this subject including the comments and memoranda submitted by Dr. John O. Nestor and Dr. John H. Moling, pediatricians in the New Drug Surveillance Branch, and Dr. Kent J. Davis, pharmacologist, Division of Toxicological Evaluation.

Certainly the two deaths in children are unfortunate occurrences but must be considered as strictly a problem of overdosage.

The fundamental basis for action in this NDA as stated by Drs. Nestor and Moling and as reflected in the new drug application are the paucity of clinical reports which form the basis for substantiating safety in this drug. We, of course, may consider action with regard to efficacy at the appropriate time. However, at this time and with the inadequate data present in the NDA both from a pharmacological (absence of studies on the full preparation) and clinical viewpoint (minimal studies performed), it would now seem advisable to consider issuance of a letter to the firm requesting immediate submission of detailed data on the cases originally submitted with the NDA and any further data that they have to substantiate safety.

If such data is not forthcoming after a reasonably short period of time, then it would appear indicated to initiate action for withdrawal of this new drug application.

MEMORANDUM

MAY 16, 1966.

To: Commissioner of Food and Drugs.
From: Robert J. Robinson, M.D., Acting Director.
Subject: IND 1454, Lomotil Pharmacologic Effects.

(G. D. Searle & Co., Chicago, Ill. (AF 13-505))

G. D. Searle & Co., sponsor of the subject IND, notified the Food and Drug Administration of discontinuance of clinical investigation of their product in a communication dated November 9, 1965. This notification followed requests for additional information in a letter dated October 22, 1965, from Frances O. Kelsey, M.D., Chief of IDB. These requests were found to be necessary after review of the submission and parts of NDA 12-462, to which we were referred, failed to support the studies outlined.

"Lomotil" is a product presently on the American market which contains in each tablet or 5 cc: Diphenoxylate hydrochloride 2.5 mg. Atropine sulfate 0.025 mg.

Diphenoxylate is chemically related to meperidine (Demerol). Reference was made to the dosage recommendation and to the animal data contained in the approved NDA (#12-462) as supporting information for the exemption. Data obtained from the NDA revealed the following facts:

1. There was no recommended dose for infants under the age of 3 months.
2. The toxicity studies in animals were done with diphenoxylate alone. There was no evidence that studies in very young animals had been done.
3. Atropine was added to the formula after all studies (animal and human) had been completed. This, apparently, was to qualify the drug as an exempt narcotic.

The IDB Medical Officer, Everlee G. Franks, M.D., recommended suspension of studies in infants under the age of 3 months pending completion and evaluation of acute, subacute and chronic toxicity studies in animals using Diphenoxylate