Explanation of the physiological effects is lacking on many drugs including aspirin.

(6) While the incidence of reported side effects is somewhat higher than we would like, it should be noted that patients reporting side effects also had diarrhea. The diarrhea existing prior to taking the drug can hardly be considered a side effect attributable to the drug, and it is questionable whether the more common side effects reported—nausea, sedation, dizziness, and vomiting—should be entirely attributed to the drug. Certainly I did not consider the side affects predominantly attributable to the drug at the time the drug was originally reviewed, nor do I do so at this time.

(7) I considered the animal safety data sufficient and satisfactory when reviewed in 1960. I see no reason for requesting any additional animal studies now. Unless there are additional data being withheld, safety is apparent from clinical experience to date. We still would not recommend the drug for very young children.

(8) It was my understanding that atropine was added primarily to make the drug less attractive to addicts. This would not have anything to do with preventing a single over dose. Some synergistic effects against diarrhea might also accrue from the atropine addition.

(9) Clinical safety and efficacy evaluations should be readily apparent after a review of the company's production and complaint records. Acceptability and repeat sales should be good indicators. since few customers are likely to continue to use a drug which either sickens them or which doesn't help their diarrhea.

(10) While the deaths of the two children are unfortunate, few drugs are "safe" when the recommended doses are exceeded by factors of thirty and fifty-two times.

(11) Most of these differences appear to be matters of professional opinion. Dr. Madigan considered the data adequate when he had to make a decision on the NDA in 1960. Dr. Nestor considers the data inadequate when reviewing it in 1964. While the NDA has deficiencies under the present standards of review, it was not considered unusual at the time it was received.

(12) We see no reason for questioning the status of this NDA 12-462 at this time unless there are additional factors involved which we are not now aware of.

KENT J. DAVIS, D.V.M.

MEMORANDUM

JUNE 18, 1966.

To: Director, Minneapolis District.
From: Fred S. Halverson, Inspector.
Subject: Adverse Drug Reaction Investigation—DPO/DRM Memo of Phone Call, June 14, 1966.

In response to the above listed memo, I visited Dr. Charles Jarvis at Childrens Hospital on June 14, 1966. Dr. Jarvis is the pathologist for Childrens Hospital.

On February 25, 1966, at 2:45 p.m., Dr. Jarvis performed an autopsy on Terrance J. Ehrich, a three-year-old white male, who had expired on February 25, 1966, at 10:10 a.m. at Children's Hospital.

Dr. Jarvis listed Diphenoxylate (Lomotil) toxicity under the "Diagnoses" section of the autopsy report. (See exhibit #1, which is the autopsy report of this case.) Dr. Jarvis stated that he attempted to obtain Lomotil toxicity data from the G. D. Searle Company, and he was not satisfied with the information they were able to provide. Exhibit # 2 is a copy of a letter of reply to a phone call made by Dr. Jarvis to the G. D. Searle Company. Dr. Jarvis had sent blood samples from the deceased to G. D. Searle for chemical analysis; and he filled out the adverse drug reaction form referred to in the letter and returned it together with a copy of the autopsy report. Exhibit #3 is a copy of a letter acknowledging a telephone call from Dr. Jarvis; a copy of a memo concerning the determination of Lomotil in the serum sample which is referred to in this letter was not available from Dr. Jarvis. He stated that he had sent this memo together with the letter which he had written to Dr. Goddard, Commissioner of the Food and Drug Administration. Dr. Jarvis feels that the child died as a direct result of an overdosage of Lomotil. He feels that the overdosage resulted from the child getting too much Lomotil, that the drug is apparently not excreted, and is accumulated to toxic levels. Dr. Jarvis gave the opinion that any pediatric medica-