Mr. STETLER. You realize when this happens, this all has to be processed through the FDA with a supplemental New Drug Application. So it is not something a manufacturer just decides to do on his own. He has to prove up again by clinical testing what happened, and then it is approved.

Mr. GORDON. That is not entirely true, either, sir. I have here some information we secured from the Food and Drug Administration, where a drug called Lomotil, which is sold by G. D. Searle & Co., had a very important ingredient added, atropine sulfate, after the FDA had accepted the original drug without it.

I ask that this information be put in the record at this point.

Senator NELSON. So ordered.

(The information referred to follows:)

SUMMARY FOR NDA 12-462

LOMOTIL

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

This review was initiated because of the reports of two fatalities in children due to overdose of Lomotil Tablets. Lomotil is put out both in the tablet form and the liquid form. Each of these doses that is one tablet or 1 teaspoonful of the liquid contains 2.5 mg. of diphenoxylate and .025 mg. of atropine sulfate. The drug is promoted for producing hypomotility of the gastro-intestinal tract primarily of course, in cases of diarrhea and dysintery.

According to the PDR of 1964, the recommended adult dose is two tablets, 3–4 times daily and for children 3–6 months of age 3 mg. daily and for children 4–12 years of age 8 mg. daily. The doses for ages in between these ranges must be interpolated. According to the labeling atropine sulfate is added to discourage deliberate overdosage but I cannot understand why this is so. Atropine sulfate is not notorious for being an emetic.

The first case reported was a 22-month-old child who received 26 tablets which contained 0.65 mg. of atropine sulfate and 65 mg. of diphenoxylate hydrochloride. The usual dose of atropine is 0.01 mg./kg./24 hours. Assuming this child weighed 11 kg. the usual daily dose would be .11 mg. He actually received 6 times this recommended dose of atropine or average dose of atropine.

The second child weighed 35 pounds (16 kg.) and received approximately 15 tablets which contained 0.375 mg. of atropine and 37.5 of diphenoxylate chloride. The usual dose of atropine to a child this size would be 0.16 hours. Therefore each of these children got an excessive dose of atropine as well.

The weight of a normal child at 3 months of age can vary from 9.8 lbs. to 16.4 lbs. depending on sex. At 6 months of age the range is from 12.7 lbs. to 20.8 lbs. At 8 years of age from 45.3 lbs. to 79.4 lbs. and at 12 years of age from 94.5 to 179 lbs. Taking the smallest size child at 3 months and the smallest at 8 years the recommended dose of atropine in this labeling would not be excessive.

With this background data on the ingredients and labeling of the drug and the two fatalities from overdose, I will now review the single volume of the NDA to determine the adequacy of the data to substantiate the safety and efficacy of this drug in all age groups. This will be reviewed in chronological order starting at the rear of the NDA with the original submission and proceeding forward to the most recent data.

Before starting this review I might point out that the original submission was on May 31, 1960 and it was found incomplete on July 29, 1960. It was subsequently made conditionaly effective on August 30, 1960 and fully effective on September 15, 1960. Subsequence of this there were several supplements.

The first paragraph is subdivided into 7 different parts. Section I appears to be a general summary of the data included in the other sections referring to diphenoxylate hydrochloride (R–1132). The descriptive formula of diphenoxylate hydrochloride (R–1132) is 2,2-diphenyl-4-(4-carbethoxy-4-phenyl-1-piperidene) butyronitrale hydrochloride. The toxicity data is briefly reviewed an it is obvious these data were obtained only from work done on this chemical entity which did