All studies cited as part of the NDA's were performed with diphenoxylate hydrochloride without atropine sulfate, which is now included in the mixture called Lomotil. The original liquid form was deleted from NDA 12–462 because of stability problems. The company modified the liquid dosage from 2.5 mg. per 4 cc., in NDA 12–699, to 2.5 mg. per 5 cc. to conform with that enumerated, in the approval as an exempt narcotic, in the Federal Register, Tuesday, July 25, 1961. The same studies used for NDA 12–462 were used in the application of NDA 12–699. Labeling remained unchanged. The drug was approved as Lomotil, (diphenoxylate hydrochloride with atropine sulfate), without any clinical, pharmacological, (animal and human) and toxicological data and studies evaluating actions, safety and efficacy of the drug as a mixture.

The company reported on 521 patients evaluated by 31 clinicians in the United States and one (1) in Belgium; 830 cases by 88 investigators in Belgium, France and the Belgium Congo. The studies were poorly controlled to uncontrolled, and testimonial as noted in an "Evaluation and Summary" by John Nestor, M.D., Vol. I (7 pages) dated 5/14/64 and Vol. II (7 pages) dated 7/21/64. G. van Dorstoppen et al, used R1132 (diphenoxylate hydrochloride) in 10 ileostomy patient's and evaluated the drug against a placebo. The drug was effective in 8 patients.

Isbell and Fraser, in a beautiful study, evaluated the abuse potential and addicting dosage for diphenoxylate hydrochloride. They found the drug non-addicting in therapeutic doses.

The clinical reports indicated that the usefulness of the drug was greatest in the diarrhea associated with the irritable bowel syndrome, (functional bowel), and in the acute diarrhea. It was least effective in the diarrhea associated with moderate to severe regional enteritis, ulcerative colitis and other inflammatory disease of the bowels. The fact of that specific modalities of therapy were used must be noted, e.g. drug, supportive and psychologic. These, in themselves, may modify the diarrhea by either ameliorating and/or curing the underlying disorder. Lomotil is only an adjuvant in the treatment of diarrhea.

The only double blind study available to me was by H. Barowsky and S. A. Schwartz, JAMA 1962. They used Lomotil tablets, placebo and camphorated tincture of opium in 40 patients with varying diarrheal disorders. They concluded that, "at varying levels of daily dosage a 2.5 mg. dose of diphenoxylate hydrochloride (1 tablet) is equivalent in antidiarrhea efficacy to 4 cc. of camphorated tincture of opium." In mild cases, Lomotil tablets gave good results with a decreasing effectiveness with increasing dosage in moderate to severe conditions. The drug was found useful in chronic diarrhea where addiction to an opiate may be undesirable.

Clinical experience, as revealed in the reference section and the letter of Davis, DVM, (FDA) of the toxicology section, indicated safety and efficacy of the drug in tablet or liquid form for adults.

There are no valid or controlled clinical studies using diphenoxylate hydrochloride with atropine sulfate in children, pregnancy or lactation. Adverse reaction of serious import involving atropine toxicity have been reported in children; 13 with recovery, 6 with deaths, overdosage with tablet and liquid forms of the drug were responsible for 14 reactions with 4 deaths. Therapeutic dose regimens accounted for 2 deaths and 4 reactions with recovery; 1 child had permanent brain damage.

Review of Labeling.—Last approval date supplement September 24, 1965 and date of insert 1960 and 1961. The last, insert of 1961 reads as follows:

"References and a more detailed discussion of Lomotil are contained in Searle Physicians Product Brochure No. 81, available from the Medical Service Dept. G. D. Searle & Company, P.O. Box 5110, Chicago 80, Illinois." "September 5, 1961". The 1961 insert is an abbreviated 1960 new Product Brochure #81.

The physicians brochure and the insert are in dire need up updating, correction, amending with additions as noted below:

1. Contraindications.
2. Precautions.
3. Adverse reactions and deaths.
4. Overdose and treatment.
5. Antidotes.
6. Elimination of dosage for children.

A partial review of the Brochure #81 and drug insert dated in 1961 reveals the following deficiencies and need for change: