3. The last paragraph of this section must be eliminated in favor of a straightforward statement such as—"This drug should not be used in children because safe indications for use have not been established and severe reactions, including fatalities, have been reported."

E. Dosage and Administration:

1. Paragraph three of this section must be eliminated in favor of a straightforward statement such as—"This drug should not be used in children because safe indications for use have not been established and severe reactions, including fatalities, have been reported."

The issuance of an Indocin (indomethacin) DRUG WARNING letter to the medical profession is necessary in view of the aforementioned package insert additions and changes, the extensive use of this drug, and the possibility of severe and fatal reactions.

[U.S. Government Memorandum]

JUNE 16, 1967.

To: R. S. McCleery, M.D., Acting Director, Division of Medical Advertising/OMR.

From: D. C. Hurwitz, M.D., Office of Drug Surveillance.

Subject: Survey of NDA Data by Dr. D. W. Englund.

I have reviewed the Indocin studies conducted by Dr. D. W. Englund contained in Volumes 4, 11, 53 and 76 of the Indocin file. The specific material reviewed consists of two copies of a speech presented before the Merck Research Institute at West Point, Pennsylvania on February 11, 1965, one letter to Merck Sharp and Dohme describing the results of clinical studies, and clinical data on 172 patients.

Dr. Englund has apparently had extensive clinical experience with Indocin, and he discussed in his speech at West Point his experiences with 550 patients using Indomethacin. At the time of this speech, Dr. Englund had been studying Indocin for two years and 50% of his total patient group had been taking the drug for eighteen months or more. Diagnostic categories included rheumatoid arthritis, rheumatoid spondylitis, psoriatic arthritis, gout, scleroderma, lupus, osteoarthritis and primary fibrositis. The author claimed good results in all groups. The largest single diagnostic category was rheumatoid arthritis in which 426 patients were treated with the drug and 362 or 85% showed "definite benefit and clinical improvement." Of 32 patients with rehumatoid spondylitis, 30 showed definite clinical improvement. The percentage improvement varies from group to group but in general the majority of patients were significantly improved.

The only data available to support Dr. Englund's contentions is contained in Volume 11 in which the raw data for 172 patients is assembled. There seems to be a representative cross section of the diseases that he has treated. The treatment period varied from one to "over forty-eight" weeks with the largest number of patients (70) having undergone treatment for 13–24 weeks. Only 22 patients received the drug for longer than 48 weeks at the time the data was compiled—March 13, 1964. Forty patients remained unreported because the investigator did not feel that they had been on the medication for sufficient time to enable evaluation.

As with most of the other Indocin studies the data consists of a clinical evaluation sheet on which various parameters are observed and an overall response to Indocin therapy graded none, poor, fair, good or excellent. In common with the other studies of this type carried out by the company, this clinical trial is completely uncontrolled and lacks the usual elements contained in a well-designed study: a placebo controlled group, random patient selection, regulation of dosage and length of administration of drug, as well as adequate and carefully designed response criteria. The study therefore has testimonial value only and in no way can be construed to show any objective evidence of efficacy of the drug in question. Unfortunately, the author's all-to-obvious bias has undoubtedly played a large role in his evaluation of the efficacy of Indocin.

In conclusion, then, one can regard this study as having only testimonial value in determining the efficacy of Indocin. While such a study has some value for preliminary use in determining whether it is worthwhile to further investigate a compound, it certainly has no definitive value in determining efficacy in this group of diseases since they do not lend themselves to easy clinical evaluation. I am able to find data for only 172 of Dr. Englund's 550 patients; it is impossible to tell at this time whether the rest of the data was submitted in another volume