NATIONAL RESEARCH COUNCIL,
Washington, D.C., April 11, 1969.

Memorandum.

To: PAC Subcommittee for the White Paper on Therapeutic Equivalence: Dr. E. B. Astwood, Dr. William B. Castle, Dr. Maxwell Finland, Dr. Chester S. Keefer.

From: Duke C. Trexler.

Subject: Editorial Comment on the White Paper in JAMA.

In a telephone call today, Dr. Hussey noted that the Journal of the American Medical Association wishes to make editorial comment on the DES white paper on therapeutic equivalence.

Dr. Hussey knows that the white paper is still in committee, and my purpose here is to invite the members of the Subcommittee to call or write me with any amendment (or with approval) of the version of the white paper that was circulated with my memorandum of April 10, 1969.

After information of these plans is given to Dr. Ley as a matter of courtesy, I will forward the white paper in the form approved by the Subcommittee to Dr. Hussey so that the proposed editorial comment can be made.

cc: Dr. R. K. Cannan
Dr. C. L. Dunham
Dr. A. Gilman
Dr. H. H. Hussey

[From American Medical News, August 4, 1969]

FDA OFFICER EXPLAINS COMBINATION DECISION

Herbert L. Ley Jr., MD, commissioner of the Food and Drug Administration, has explained why the FDA deleted novobiocin-tetracycline combination drugs, and calcium novobiocin-sulfamethiozole tablets from the acceptable list in the *Federal Register*.

Dr. Ley explained the reasoning in a letter written to Ernest B. Howard, MD, executive vice president of the American Medical Association.

In his letter, Dr. Ley noted that the National Academy of Sciences' Drug Efficacy Study Group had recommended to the FDA, "after reviewing all data the manufacturer submitted to the group to support its claims of efficacy for the products, that tetracycline-novobiocin and sulfamethiozole-novobiocin were ineffective as fixed combinations."

Dr. Ley said the study concluded that "there is a lack of substantial evidence that the drugs will have the effectiveness they purport and are represented to have, and more particularly, that each ingredient in the . . . combinations contributes to the claimed clinical effect of the drugs."

Dr. Ley emphasized the FDA action was not based entirely on the study group's findings. "We considered the views of such authorities as Louis Weinstein, as published in Goodman and Gilman's textbook. We visited Upjohn to obtain any materials from its files that might support the effectiveness claims. And we met with Upjohn's management and medical people.

"Finally," said Dr. Ley, "we had a report from the NAS/NRC on novobiocin itself which required a basic revision of the prescribing information for the drug, limiting its use and emphasizing its hazards.

"From all of this," Dr. Ley declared, "it clearly appeared that there are no adequate and well-controlled investigations for which experts could conclude that the combination drugs will support the effectiveness claimed."

He pointed out the Administration told Upjohn representatives last May that "we were aware of 53 adverse reactions to Panalba, including three fatal blood dyscrasies, one fatal Stevens-Johnson syndrome, and a variety of other sensitization reactions and reports of jaundice and liver damage following Panalba administration."

In referring to some of the reported cases, Dr. Ley said that "While a positive cause and effect relationship between reaction and drugs sometimes is difficult to establish, this is not the case for most of the above reactions."

Dr. Ley stressed, however, that "as the American Medical Association is well aware, adverse drug reactions are grossly under-reported, so we have no way of estimating the true incidence rate of adverse reactions to Panalba."