MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
September 13, 1968.

To: Philip R. Lee, M.D.
From: Milton Silverman, Ph. D.
Subject: Bibliography on Biopharmaceutics.

On August 5, 1968, the Pharmaceutical Manufacturers Association released a publication entitled *Bibliography on Biopharmaceutics*, citing 501 references on the influence of pharmaceutical formulation upon the therapeutic activity of drugs.

In an accompanying news release, a PMA spokesman stated: "This unique publication refutes the astonishing myth that there are not significant differences among dosage forms of the same drug."

This statement in itself is somewhat astonishing. Among responsible scientists and clinicians, we are not aware of any doubt that there may be significant differences. The important question is how often these differences occur, and what threat they pose to the welfare of patients.

Here it is important to agree on the groundrules for the analysis—obviously, there will usually be substantial cilnical differences between two products in different dosage forms, such as one in solution and one in tablets, or one in a coated tablet and one in an uncoated tablet.

But that is not the issue. The important question is whether or not there will be clinically important differences when two different products, containing essentially the same amounts of the identical active ingredients, in the same dosage form, both meeting USP, NF or other official standards, are administrated in the same way—and whether this can be demonstrated in human subjects through properly designed, valid experiments.

With this in mind, it seemed desirable for the Task Force, its consultants, and the Food and Drug Administration, to review the new publication, with its 501 references. The following points were obvious:

Of the 501 references, only 221 were actually conducted in human subjects.

Of the 221, only 76 were—by PMA's own evaluaton—"adequately designed or controlled" experiments.

Of these 76, only 12 represented comparisons between what might seem to be different brands of the same chemical equivalents.

And of these final 12, most compared different dosage forms (such as tablets versus effervescent solutions), or different salts (such as sodium derivatives versus potassium derivatives), or different coatings (such as delayed release products versus rapid release products). Some of these final products failed to meet existing USP or NF standards, and thus would be illegally on the U.S. market.

At the most, Task Force staff and our consultants agree, there were only two or three which demonstrated statistically-significant lack of biological equivalency, and in one case, the differences were described as being without any practical clinical importance.

In summary, it seems evident that the new publication represents a useful compilation of the literature on this subject.

The finding that only two or three of the 501 citations in this book indicate significant lack of clinical equivalency would seem to be consistent with the Task Force statement that "lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health."

Dr. LEE. Mr. Chairman, I have tried to suggest several of the major issues pertaining to the use of prescription drugs which both your subcommittee and the Secretary's task force have examined in very considerable detail. As you know, the work of the task force—like that of the subcommittee—has been much more extensive than is reflected in my presentation. And our work is continuing, leading, as I have indicated, toward recommendations on the vitally important—indeed central—question of including under medicare coverage of the cost of out-of-hospital prescription drug costs. This