Thus the variations denoted in the articles of this bibliography, whether subtle or pronounced, can have significant effects in patients."

"It is interesting to note," the PMA executive added, "that the extensive research required for this study failed to turn up a single reference establishing that all formulations of the same drug from a variety of sources are equivalent—or even probably equivalent. Yet this invalid assumption has been made repeatedly in proposed legislation at both state and federal levels."

Studies in the compilation indicate that drug uniformity cannot be established simply by testing the end product.

"Thus compliance with such standards as the United States Pharmacopoeia and the National Formulary is no guarantee of product effectiveness in actual patients," Mr. Stetler asserted. "This is not to imply any criticism of the USP and the NF, both of which have done outstanding work in developing drug standards. But it is to say that therapeutic equivalence can only be shown in the clinic or by well-designed *in vivo* or *in vitro* presumptive testing, complex and exceedingly costly as this may be."

"In the final analysis, the excellence of a product must depend upon the excellence of the manufacturer. There are no substitutes for quality control of a high order and consistently good manufacturing practices," Mr. Stetler said.

The PMA president pointed out that because of budget and manpower the FDA concentrates its inspections in major company plants, being unable to give much attention to the smaller firms that have the greatest number of product recalls.

"Yet member firms of the PMA, producing 95 percent of the nation's prescription drug supply, have only 20 percent of the recalls. Companies making only five percent of available drugs are identified with 80 percent of the recalls despite little regulatory attention. Such a record should be a warning to those who blandly assume the equivalency of drugs produced under a variety of conditions," he stated.

"To deny that formulation is important is to deny the very basis of the profession of pharmacy," Mr. Stetler said.

Of the 501 citations in the bibliography, 221 cover *in vivo* human studies, with the remainder concerned with studies in animals as well as *in vitro*. About 20 percent appeared originally in the *Journal of Pharmaceutical Sciences* of the American Pharmaceutical Association.

"It should be borne in mind," the preface to the bibliography states, "that there is a massive body of information concerned with such subjects as: the stability of an active ingredient in a pharmaceutical formulation and the stability of the formulation itself as well as with preservatives, sterility, flavors, and other significant pharmaceutical factors which ultimately affect the therapeutic activity of a drug. Articles on these topics, however, were generally excluded..."

(Definition of biopharmaceutics: a field encompassing the study of the relations between the nature and intensity of the biological effects observed in animals and man and the following factors—the nature of the form of a drug, such as ester or salt; the physical state, particle size and surface area; the presence or absence of adjuvants; the type of dosage form; and the pharmaceutical process used in manufacturing).

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., September 24, 1968.

Hon. GAYLORD NELSON,
Chairman, Subcommittee on Monopoly, Select Committee on Small Business, U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: I have asked the professional staff of the Department's Task Force on Prescription Drugs to review the Pharmaceutical Manufacturers Association publication, *Bibliography on Biopharmaceutics*, as requested in your letter of September 9.

I am enclosing for your information a report prepared by the Task Force staff director, Dr. Milton Silverman.

Sincerely,

WILBUR COHEN, *Secretary.*