be justified so that the consumer and the prescribing physician are not forced to use an expensive and irrational combination when a single, inexpensive drug may do equally well or better.

That is essentially my testimony.

(The complete prepared statement and curriculum vitae of Dr. Kunin follows:)

STATEMENT OF DR. CALVIN M. KUNIN, CHAIRMAN, DEPARTMENT OF PREVENTIVE MEDICINE, UNIVERSITY OF VIRGINIA

Senator Nelson and Members of the Committee, I am pleased to have the opportunity to present my opinions before this Committee once again. You may recall that I testified before you on August 8, 1967, concerning problems related to promotion of drugs. My curriculum vitae is attached to this statement.

My current task is to discuss the problem of use of fixed dosage combinations of antibiotics. As you may know, I served as chairman of Anti-Infective Panel IV of the National Academy of Science-National Research Council during its review of over 3,000 drugs licensed between 1938 and 1962. The other Panel chairmen are also testifying before this Committee. I would expect that some of my comments will overlap theirs. I believe, however, that you will find a great deal of unanimity among us.

It is important to emphasize that the task of our various Panels was to review various drugs for efficacy based on the literature, information supplied by the manufacturer, consultation with respected colleagues, and personal observation. Our review was focused on the claims made for the product as stated in the package insert. We did not attempt to assess relative efficacy of drugs nor were we concerned with relative cost to the patient.

Guidelines for our work were set down by the Policy Advisory Committee of the NAS–NRC study. Initially, four categories were selected: effective, probably effective, possibly effective, and ineffective. These judgments were made for each individual claim and were supported by extensive comments and citation of the pertinent literature. Judgments were then transmitted to the Food and Drug Administration for appropriate action.

During the course of our deliberations, it became evident that a fifth category was required to handle the question of fixed combinations of antimicrobial agents. This category, e.g., ineffective as a fixed combination, was defined as the combination is no more effective than any one of its active ingredients. Some liberty was taken with the original guidelines since one could have also judged the combinations as "effective but. . ." with a long comment noting why the particular claim was not warranted. In any even, "ineffective as a fixed combination" or "effective but. . ." really say the same thing, but the former emphasizes the point we wished to make.

Fixed dose combinations have been on the market for some ttime. The logic used by the manufacturers is based on one or more of the following arguments:

(1) Combinations could provide broader antimicrobial spectrum or coverage. This would presumably serve to catch organisms before definitive bacteriologic information and sensitivity tests were available,

(2) Combinations might act in a synergistic fashion, that is, the efficacy of the combination is greater than the sum of its parts,

(3) Combinations could provide greater convenience, that is, only one dosage form or injection would be needed,

(4) Combinations would delay the appearance of resistant mutant strains,

(5) Certain combinations might prevent side reactions induced by the active ingredients,

(6) Certain combinations might aid symptoms at the same time they were destroying bacteria.

Each of these points seem reasonable on face value, but our task was to examine the evidence that this was indeed the case for specific combinations. I believe that it is important to emphasize here that each claim must be examined on its individual merits.

My own Panel, together with Anti-infective Panel II, chaired by Dr. William Hewitt, Professor of Medicine at UCLA medical school, jointly considered fixed combinations of penicillin and streptomycin and penicillin and sulfonamides. We presented our judgments to the FDA based on claims made for them that these were ineffective as fixed combinations. We felt that the issues involved were so