The magnitude of this study and the complexity of the decisions involved can hardly be overestimated. Since October 1967, the panels have submitted to FDA 2,824 reports covering approximately 3,700 drug formulations manufactured by 237 companies. About two-thirds of the products could be handled by a single panel, but the remainder, because of the multiplicity of therapeutic indications, had to be reviewed separately by 2 to 15 panels. The Academy has estimated that 10,000 or more therapeutic judgments were required. Panelists spent about 10,000 man hours in meetings, in addition to the time required for preparatory work.

The responsibility for evaluating and carrying out the Academy recommendations is, of course, FDA's. In January 1968, we established a special Task Force in the Bureau of Medicine to handle this difficult assignment. The procedures we had decided upon for implementing the recommendations were explained at a public meeting that same month.

We encountered many complex and time-consuming problems in the process of translating Academy recommendations into Agency actions. First, there is the sheer volume of handling more than 10,000 therapeutic judgments. Different panels that reviewed the same drug did not always use the same terms in describing its effects and consultation with the various panel chairmen frequently was necessary.

The Academy panels considered only the medical aspects of the drugs reviewed, but FDA must consider regulatory responsibilities as well. For many products, this involved translating panel recommendations into completely new or revised labeling, frequently covering a large number of indications. In this process, we must also be sure that the new language is consistent with other labeling.

Despite these problems and others, we have developed procedures for implementing Academy reports which I believe are orderly, rational, and logical. These procedures have evolved from our experience in handling the reports and they are by no means static. Procedures will be changed as necessary to deal with any problems that may arise.

At the present time, our Task Force makes a preliminary screening of panel reports to determine the Division within the Bureau of Medicine which can best handle the drugs involved. The Task Force sets a deadline for completion of the evaluation and the preparation of labeling by the appropriate Division. Priorities as to the order of evaluation are based upon—

1. Safety, direct or indirect.
2. Therapeutic significance of the drug (or class of drugs).
3. Volume of use of the product.

After we have determined the action necessary to carry out NAS recommendations, public notice is given in the *Federal Register* of FDA's conclusions and the subsequent steps to be taken.

If a drug is found "effective," of course, no subsequent steps may be necessary.

For those drugs found "probably effective," we give the manufacturers 12 additional months to provide data to support their claims.

For those drugs found "possibly effective," we allow six months for the submission of such data.

For drugs ruled "ineffective," we allow 30 days for the submission of any evidence that may have been overlooked to support efficacy claims.

The manufacturer of a drug falling in the "effective, but," category is told what labeling or formulation change is required to meet the recommendations of the NAS panel. Depending upon the action the firm elects to take, the drug will fall into one of the other four categories, and the appropriate time limit would apply.

If the companies do not provide the required evidence of efficacy, FDA then initiates action to withdraw approval of the new drug application or, in the case of antibiotics, to repeal the applicable regulations which permit the products to be marketed. Companies have the opportunity to reqeust and show reasonable grounds for a public hearing, but whether the drug will be permitted to remain on the market during the course of a hearing depends on the degree of hazard which its continued distribution may present to patients.

In the summer of 1968, we began to receive the NAS/NRC reports on the antibiotic combination drugs. The conclusions of the Academy panels were in line with what experts in the antibiotic field, and pharmacology textbooks, such as *The Pharmacological Basis of Therapeutics* by Goodman Gilman, had been saying for years.