The study was carried out under the direction of the Division of Medical Sciences of the NAS/NRC. This Division's Drug Research Board, with additional representatives to cover all appropriate medical specialties, made up the Policy Advisory Committee (PAC) that established guidelines for the review.

In the development of guidelines for the study, the Academy and the PAC made an effort to involve the pharmaceutical and medical communities to the greatest possible extent. A broadly representative forum was held on the guidelines prior to their adoption by the PAC. Among the other matters covered, the guidelines provided that:

"The judgments of the Panels will be based on the following criteria: (1) factual information that is freely available in the scientific literature, (2) factual information that is available from the FDA, from the manufacturer or other sources, or (3) on the experience and informed judgment of the members of the Panels."

Operating within these criteria, the panels were asked originally to classify claims for drugs into one of four categories:

(a) *Effective.*—For the presented indication, the drug is effective on the basis of the criteria which the panel has established for its review.

(b) *Probably Effective.*—For the indication presented, effectiveness is probable on the basis of the operative criteria, but additional evidence is required before it can be assigned to category (a).

(c) *Possibly Effective.*—In relation to the indication in question, there is little evidence of effectiveness under any of the operative criteria.

(d) *Ineffective.*—In relation to the indication in question, the panel concludes that there is no acceptable evidence under any of the operative criteria to support a claim of effectiveness.

During the course of the study, it proved necessary to add two additional categories. One of these, "effective, but," was added to accommodate those drugs which presented special problems such as products which were found effective for the indications listed, but which included ingredients, represented as active, which were concluded to be ineffective, and for products that were effective but required labeling revisions. The second category added was "ineffective as a fixed combination," a classification I will discuss in greater detail a little bit later.

In support of each category assignment, panels were expected to present a justification citing the scope of the evidence evaluated and, where appropriate, how this evidence supported the decision. It was evident that these justifications would be of great value to FDA in effecting by regulatory action the recommendations of NAS/NRC. It should be noted that NAS/NRC committees were not charged with the review of safety of the products.

To enable NAS/NRC to proceed with its task, it was necessary to provide the panels with the basic information material on each drug to be evaluated. On July 9, 1966, the FDA published an order in the *Federal Register* calling for each holder of a new drug application approved between 1938 and 1962 to submit specified information on each drug, preferably on forms prepared by NAS/NRC. The information requested included an identification of the product, copies of the labeling to be reviewed, and a list of literature references most pertinent to an evaluation of the effectiveness of the drug. The submission of unpublished articles or other data appropriate for the same purpose was also invited. This procedure gave the sponsors the opportunity to identify the evidence which they believed supported claims made for the drugs. In October 1966, the same procedure was initiated to include in the Drug Efficacy Study antibiotics which had been accepted for certification prior to 1962. A small staff at FDA was responsible for the recording and transmission of these reports to the Academy. This included the assignment of each drug to one or more therapeutic categories. These categories had been previously designated by an ad hoc committee appointed by NAS–NRC.

The staff at NAS–NRC and the PAC did a superb organizational job in preparation for the study. Twenty-seven panels, comprised of experts in medical centers throughout the country, were appointed to cover 21 therapeutic categories of drugs. In the course of the study it became necessary to increase the number of panels to 30 and the drug categories to 22. With a chairman and five other members on each panel, plus consultants obtained for special problems, a body of approximately 200 experts conducted the reviews. FDA assigned 10, and later 11, Public Health Service medical officers to serve as executive secretaries for the 30 panels.

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