I subsequently notified both firms that we were considering cancellation of the time extensions granted in January, and directed them to immediately submit any substantial medical evidence they had that would be relevant to the efficacy of the drugs. Additional data were provided, but these were not adequate to demonstrate the effectiveness of the fixed combinations. Upjohn presented a proposed protocol to develop the type of evidence required by law, but explained that it would be quite costly and would require about two years for completion.

Another significant antibiotic action was coming to a head about this same time. Our final review of the Academy's reports on novobiocin indicated that marked revisions in the labeling were imperative, not only from the standpoint of efficacy, but on grounds of safety. On May 2, 1969, we published in the *Federal Register* the new labeling to be required for this antibiotic, including a prominent "warning box" citing the frequency of adverse reactions—liver malfunctions, and rashes, and the occurrence of a more serious type of reaction, blood dyscrasias. I submit a copy of this *Federal Register* announcement for the record.

On May 1, 1969, the day this announcement was made public, representatives of the Upjohn Company came in at my request to discuss the steps to be taken in regard to novobiocin. Upjohn markets this antibiotic as Albamycin. In addition, both Panalba and Albamycin-T, which we had ruled ineffective as fixed combinations, contain novobiocin as an ingredient.

At this meeting, we advised the firm that we had stopped certification of new lots and we proposed the following steps with regard to Albamycin:

1. That the company issue a letter to all physicians within 10 days describing the new warnings and restrictions on use.
2. Prompt printing of the new labeling.
3. Recall to the user level of all outstanding stocks of novobiocin, both oral and parenteral, with replacement to be made by May 31, 1969, with stocks carrying the new labeling.

With respect to the combinations containing novobiocin, we advised the firm that we had stopped the certification for new lots and we proposed:

1. Decertification of all outstanding stocks of the drugs.
2. Prompt recall to the user level of these outstanding stocks.
3. A report on the status of the combination products in the "Dear Doctor" letter on novobiocin.

We discussed with the Upjohn representatives the company's inability even now to produce or to point to any medical support for their efficacy claims that would satisfy the legal requirements.

I regret to say that the firm, up to now, has taken only one of the steps outlined—it has agreed to the submission of labeling for Novobiocin. We were, therefore, obliged to proceed in other ways to carry out the decisions which I strongly believe are necessary to protect the public health. I submit a copy of the new labeling for the record. We are prepared to certify batches of Novobiocin with this labeling; this does not, however, alter our position that previously certified stocks of Novobiocin distributed with the old labeling must be taken off the market.

On May 15, 1969, we published an order in the *Federal Register* repealing the antibiotic regulations for Panalba and Albamycin-T and decertifying outstanding stocks. These preparations will be subject to seizure when the order becomes effective on June 14, 1969. We set the effective date 30 days after publication to allow the firm to make objections, to show reasonable grounds for a hearing, if it has such grounds, and to give the firm time enough to recall stocks of these products. Upjohn has not initiated these recalls, however.

The firm's position is that these products should not be removed from the market without a public hearing. If reasonable grounds are presented, we would be required to grant a hearing on the efficacy of the preparations—but we do not believe they should remain on the market during the course of a hearing and any subsequent litigation that might ensue. In the light of the hazards involved and the NAS–NRC finding that the products are ineffective as fixed combinations, continued marketing cannot be justified.

I have described in some detail the Agency's actions affecting Novobiocin, and combinations including Novobiocin, because we intend to follow the same pattern in dealing with other antibiotic preparations reviewed by NAS–NRC.

The Committee should understand that reports on other antibiotic combinations were coming to my office from the Bureau of Medicine Task Force during this same period of time. On April 2, 1969, we announced in the *Federal Register*