You will note that as part of their review, the Panels commented on the literature references submitted by the manufacturer in justification of its claims, as well as other published studies. They concluded that there is "a lack of substantial evidence that the drugs will have the effectiveness they purport and are represented to have, and more particularly, that each ingredient in the . . . combinations contributes to the claimed clinical effect of the drugs."

They concluded also that a "disadvantage of this fixed combination is the inadequate amount of novobiocin present," 125 mg., and that novobiocin has a "narrow antibacterial spectrum" that does not significantly enhance the effectiveness spectrum of the tetracycline or sulfamethizole components of the products.

Our decision to delete these antibiotic combinations from the list of drugs acceptable for certification was not based solely on the recommendations of the NAS/NRC Drug Efficacy Study Group. We considered the views of such authorities as Louis Weinstein, as published in Goodman and Gilman's textbook. We visited Upjohn to obtain any materials from its files that might support the effectiveness claims. And we met with Upjohn's management and medical people on the question whether any substantial medical evidence was available to justify the promotional claims.

Finally, we had a report from the NAS/NRC on novobiocin itself which required a basic revision of the prescribing information for the drug, limiting its use and emphasizing its hazards. From all of this it clearly appeared that there are no adequate and well-controlled investigations for which experts could conclude that the combination drugs will support the effectiveness claimed.

On June 16, the company filed objections to the withdrawal order and presented 50 papers which it said contained substantial evidence. A review of most of the papers by the FDA advisory committee on anti-effective agents showed they did not provide any evidence of effectiveness. The remaining papers are under review.

Moreover, this Administration was increasingly concerned about the toxicity of these combinations in relation to their usefulness. As we informed the Upjohn Company representatives on May 1, 1969, we were aware of 53 adverse reactions to Panalba, including 3 fatal blood dyscrasia, 1 fatal Stevens-Johnson syndrome, and a variety of other sensitization reactions and reports of jaundice and liver damage following Panalba administration.

A further search of FDA files, covering the period from the time of initial marketing of Panalba up to 1964, has disclosed 7 additional blood dyscrasia cases, 10 more gastrointestinal disturbances, 2 more liver damage cases, and 27 additional miscellaneous adverse reaction cases. The total adverse reactions reported from Panalba to the Food and Drug Administration to date are as follows:

Blood Dyscrasias (8 fatal)	19
Gastrointestinal disurbances	20
Skin reactions (rashes, etc.)	12
Oral (including tooth discolorations)	12
Liver disturbances (1 fatal)	4
Miscellaneous (including sensitization reactions) (2 fatal)	43
Total (11 fatal)	110

Significantly, the blood dyscrasia cases make up over 70% of the fatalities and the fatalities make up 10% of the total reports known to FDA. And since the combinations offer no significant benefits, even a small number of unnecessary fatalities is a reason for taking corrective action.

While a positive cause and effect relationship between reaction and drugs sometimes is difficult to establish, this is not the case for most of the above reactions.

One case reported to us by Upjohn in 1964 serves to illustrate at least two of the reactions which we know Panalba to cause:

A 2½-year-old boy was treated by his doctor for tonsillitis with Penalba suspension, one teaspoon four times daily. Two days later, he developed a rash on the entire body. His doctor gave him an injection of penicillin. He had received penicillin before, without untoward effect. That evening, the rash became purpuric, his temperature rose to 104°, and he was hospitalized. Studies of his bone marrow showed marked depression of all cells, and despite transfusions, he died after six days, with what his physician described as "complete destruction of the bone marrow," aplastic anemia.