These recommendations were implemented by the Bureau of Medicine and used as the basis for developing the final labeling for all three dicloxacillin products manufactured by Wyeth, Ayerst, and Bristol.

At a September 12 conference, a statement seemingly agreeable to both Bristol and FDA was composed, and on September 19, Bristol submitted proposed package inserts. However, under indications two additional paragraphs were added by the company which pertained to the development of resistant strains. On October 19, 1967, FDA wrote Bristol that approval of these changes in the package inserts could not be given.

Further telephone conversations took place in November, December, and January; and on February 23, 1968, a conference was held between Bristol and FDA at which Bristol again presented its position on resistant staphylococci. The company presented additional data in which it was demonstrated that among Bristol's employees, exposure to semisynthetic penicillins had not been associated with any nasal carriage of methicillin-resistant staphylococci aureus. It was pointed out that the data did not seem pertinent to the past major issues. Further, they were informed that the other two producers of dicloxacillin had now submitted labeling conforming to all FDA requests, and that these would be acted upon.

On February 26, 1968, Bristol submitted revised labeling for dicloxacillin which conformed to the wording requested by FDA. They expressed disagreement with the switch statement wording, but agreed to accept it. They submitted corrected package inserts on March 5, 1968.

On March 8, 1968, Dr. Ley, the then Director of the Bureau of Medicine, was notified that the Division of Anti-Infective Drugs recommended approval of the application of Bristol for sodium dicloxacillin, and that the labeling submitted was acceptable. (Similar approvals were recommended for the sodium dicloxacillin applications of Ayerst and Wyeth on that date.)

However, the company's activity took a new direction. About a month later, on April 9, 1968, the Surgeon General of the Public Health Service, Dr. William H. Stewart, acting for Dr. Philip Lee, Assistant Secretary of Health, Education, and Welfare, received a position paper critical of our actions from Mr. Thomas Corcoran, an attorney for Bristol.

We were asked to comment on that position paper, a copy of which is enclosed for the record—exhibit A.

Senator NELSON. It will be printed in the record.

(The document referred to follows:)

EXHIBIT A

The FDA has a theory (hereinafter called the reserve drug theory) that some antibiotics should be limited for use only in the treatment of resistant staphylococci infections even though some antibiotics are also concededly effective for the treatment of infections due to streptococci, pneumococci and non-resistant staphylococci. The FDA has implemented this theory by demanding that the labeling for these antibiotics (which are semi-synthetic penicillinase-resistant penicillins such as oxacillin, naficillin, cloxacillin and most recently dicloxacillin which is awaiting FDA clearance) state in effect that if laboratory tests determine that the infection is caused by organisms that can be treated by the old line penicillin or penicillin G, the physician must be advised to stop using the semi-synthetic penicillinase-resistant penicillin.