On July 12, 1966, FDA wrote Bristol advising that, in order to bring proposed labeling for dicloxacillin into conformity with that of the other penicillinase-resistant, semisynthetic penicillins, the following sentence should appear in capitals or bold face at the beginning of the "Indications" section. "Hypen"—which was their proposed name at that time "is particularly suitable against infections due to staphylococci resistant to penicillin G (or phenethicillin)," and that, in addition, the following should appear in the same section: "If it is determined that the infection is not due to a penicillin G-resistant staphylococcus, a change to penicillin G or phenethicillin may be considered." This statement referring to changing or "switching" antibiotics I will refer to hereafter as the "switch" statement.

On July 13, 1966, Bristol replied, in part: "We still feel that * * * such a statement (the switch statement) is not justified by the facts. We will continue to accumulate data and will bring this to your attention as more experience becomes available so that we may review it again." However, the labeling accompanying this letter incorporated the FDA recommendations.

On July 29, 1966, Bristol submitted revised draft labeling incorporating three minor changes requested by an FDA telephone conversation. Bristol also changed the trade name of the drug to "Dynapen."

About that same time in 1966, Bristol was promoting its semisynthetic Tegopen (sodium cloxacillin monohydrate) with an advertising theme that is was an "everyday penicillin," and depicting its use in routine office practice. In October, we publicly criticized this ad campaign as offering the drug for conditions for which it had not been approved. Bristol representatives visited with us, contending that the drug was indeed suitable for everyday use, and they were told that before such a range of usefulness could be approved the company would have to provide the medical justification for labeling changes to permit it.

On November 25, 1966, Bristol submitted proposed revised labeling for their already marketed antibiotic, Tegopen (sodium cloxacillin monohydrate). In this, they had deleted the statement advising that therapy be switched to penicillin G in the event that bacteriological studies show the infecting organism not to be a penicillinase-producing staphylococcus. They made it clear that they intended this change also to apply to dicloxacillin. This submission was followed in January 1967 by a marketing report for a number of penicillins, a report intended to support Bristol's contentions that the incidence of resistant staphylococci had not risen despite widespread use of the semisynthetics.

In an attempt to resolve the labeling of dicloxacillin, the FDA, more than a year ago, sent a questionnaire to 11 recognized experts in the field of microbiology and antimicrobial therapy. Among the questions asked, two dealt directly with the problem of so-called "restrictive" use.

1. "Do you believe that penicillinase-resistant penicillins are now the drugs of choice for the routine treatment of all infections caused by Gram-positive cocci susceptible to their actions?" All 11 experts answered "No."

2. "Assuming you have initiated chemotherapy with a penicillinase-resistant penicillin in a severe infection and the patent is showing excellent clinical response but the cultures now show the causative or-