September 12, 1966.—Telephone conversation between Dr. H. Peltier (Bristol) and Dr. A. E. Smith (FDA). Dr. Smith recommended that in the dosage section of the proposed package insert the words "of the upper respiratory tract" be placed after "mild to moderate infections" and the phrase "higher and more frequent dosage in more severe infections and in infections due to penicillinase producing staphylococci" be inserted.

September 12, 1966.—Submission by Bristol of package circulars incorporating the changes suggested by Dr. Smith (9/12/66).

September 18, 1966.—Submission by Bristol of 111 case reports of patients treated at a dose of 12.5 mg./kg. or less per day and 14 cases treated at doses of 12.5 mg./kg. to 17 mg./kg./per day The sponsor claims that all but one patient were bacteriologically cured and offers the following points with reference to use of these doses: 1) The average MIC's for dicloxacillin *in vitro* range from 0.016 to 0.3 mcg./ml. 2) After administration of an oral dose of 125 mg. to an adult, peak serum levels are considerably higher than the highest MIC's of sensitive organisms. 3) Although the drug is considered to be highly bound *in virto* (by serum proteins) the clinical significance of this binding is not known, particularly in view of the rapid excretion and short half-life of the drug. 4) The cases presented offer clinical and bacteriological evidence that the drug is effective in mild to moderate respiratory infections at the recommended dose. 5) Additionally, the 117 staphylococcal infections treated of which 80 were treated at 12.5 mg./kg. or less per 24 hours (including 46 of the 80 due to penicillinase-producing staphylococci) indicate that the agent is highly effective in these infections as well. However, we will accede to your request to gather more data on the treatment of patients infected with penicillinase-producing staphylococci at the low dose.

October 10, 1966.—Letter from FDA to Bristol concerning experience with the assay procedure for dicloxacillin. The recommended infrared method was found to use up too much of the standard and a modification is proposed.

October 12, 1966.—Conference between FDA and Bristol called to discuss Bristol's revised clinical protocol for evaluation of dicloxacillin 125 mg. tablets in streptococcal infections. Under this protocol, cultures are to be taken before therapy, and 48–72 hours following its termination. FDA advised that the least number of laboratory studies which would be acceptable is a white count, hematocrit and urinalysis in each case and that complete specification of the bacteriological methods used should be provided.

November 25, 1966.—Submission by Bristol of revised labeling for Tegopen (sodium cloxacillin monohydrate). In this, 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 is deleted. The reasons given for this change are intended by the sponsor to apply also to dicloxacillin, and are as follows: "1) Clinical data obtained to date demonstrates that cloxacillin is safe and effective when used in the treatment of infections due to Group A streptococci, pneumococci and nonpenicillinase-producing strains of staphylococci. 2) It may be ill-advised to change therapy if a staphylococcus initially moderately sensitive to penicillin has been treated with cloxacillin since such an organism might have become more resistant in the interval before the bacteriology results were obtained. 3) There is no evidence from available data to support the development of resistance by staphylococci to the penicillinase-resistant penicillins. In the period during which methicillin has been commercially available, there has been no increase in the incidence of staphylococcal strains resistant to the drug. When resistance does occur, there is no evidence that it is related to exposure to methicillin. If resistance were to develop through a process of mutation, it would be reasonable to have expected a slow but inexorable increase in the percentage of resistant strains during the last six years, probably with outbreaks of resistant staphylococcal infections in individual hospitals or wards. Since neither of these events has occurred, we submit that this constitutes further evidence to support our position."

December 21, 1966.—Submission by Bristol of pathologist's report on the testes of male rats used in teratology studies on dicloxacillin. This report states that all sections were within normal limits and that the treated and control groups were not distinguishable.

January 6, 1967.—Submission by Bristol explaining that in view of difficulties encountered in previous teratological studies with mice, another study had been performed. This study demonstrates that there was no difference between dicloxacillin and penicillin V with regard to parental or fetal findings. No adverse changes with respect to viability, number of pups born, resorption sites or ab-