Cases of staphylococcal infections treated with oral dicloxacillin have been reviewed. Doses of 1 gram daily in divided doses seem to provide adequate therapy for these infections when combined with other appropriate treatment (i.e. surgery). A very low rate of side effects and no serious complications occurred in 148 patients. The evidence available supports the use of low doses (125 mg. q.i.d. of 12.5 mg/kg/day) in mild and localized infections.

The majority of pneumococcal infections reported in the Form 5 were pneumonias. 250 mg. q.i.d. seems to be the lowest adequate dose for this infection. It may be expected that minor and localized pneumococcal infections will respond to lower doses, but few of these were reported and considered acceptable.

The data strongly supports the efficacy of dicloxacillin, 125 mg. q.i.d. or 12.5 mg/kg/day orally, in treating mild to moderate upper respiratory infections due to betahemolytic *Streptococcus pyogenes*. Cures were obtained in over 95% of cases and no instance of post-streptococcal complication or adverse reaction occurred.

March 29, 1967.—Initial pharmacology review of Form 5. A summary of this review by Dr. Orthoefer (FDA) follows:

Structurally, dicloxacillin differs from cloxacillin and oxacillin only in the number of chlorine atoms present in the side chain of the 6–APA molecule. It shares many biological properties with these acid stable penicillin, including their relative low toxicity and adequacy of blood levels obtainable by oral administration.

As with other penicillin compounds, rabbits and guinea pigs suffer a high mortality following treatment with relatively small oral doses of the drug. . . . This is usually attributed to an upset of the normal gastrointestinal flora of these animals leading to toxic manifestations and death. The data presented indicated that dicloxacillin and nafcillin produce somewhat more gastrointestinal damage in these species than other penicillins. . . .

The disastrous effects of dicloxacillin on the dams makes interpretation of the rabbit teratology study, in terms of effects on the fetus, extremely difficult. However, no consistent trends were noted in mouse teratology studies and a 2-litter reproduction study in rats yielded no remarkable evidence of adverse effects.

The rat and dog studies revealed no unusual findings. Dosage levels of over 20 times the proposed human dose were administered to these animals for 12 weeks without adverse effects. Other studies in our files (Ayerst) have shown that dogs can tolerate 500 mg. kg for 6 months and 1000 mg/kg for 2 weeks without adverse effects.

The urinary excretion rate of dicloxacillin for man and dog differ significantly. In human studies 40–75% of a given dose was excreted in the urine within 6 hours . . . in the dog less than 2% is excreted . . . within 4 hours. . . . This difference may be explained by percent protein binding or by a greater metabolism of the drug in the dog.

The data submitted thus far indicate that dicloxacillin capsules are acceptable from a safety standpoint providing all precautions pertaining to penicillin are clearly stated in the labeling.

March 30, 1967.—Conference between Bristol and FDA on labeling. Minor revisions were requested by FDA and agreed to by Dr. Peltier. In their summary, Drs. Smith and Anderson (FDA) state that with these changes, labeling is acceptable.

March 31, 1967.—Telephone conversation between FDA and Bristol concerning controls. With Bristol's agreement to use a minimum potency limit of 850 mcg./mg. for the bulk drug and a dose of 20 mg. for the toxicity, Mr. Norton (FDA) states that "all points of controversy have been resolved."

March 31, 1967.—Drug control review notes state that controls are adequate.

March 31, 1967.—Briefing memorandum by Dr. H. C. Anderson (FDA) concerning dicloxacillin. Dr. Anderson cites the medical officer's reviews of 7/14/66 and 3/28/67 as support for the safety and efficacy of dicloxacillin. The results of a poll of specialists conducted by FDA on the question of labeling for dicloxacillin is discussed as follows:

"We polled a number of specialists in the field of infectious disease and they would agree in large part to the old form of labeling. However, it is my feeling that we sampled a very biased group of individuals, almost none of whom would in their academic work see or treat many of the diseases (streptococcal pharyngitis, bronchitis, superficial skin infections) for which these drugs are advocated. I am in complete agreement with (Dr. Peltier's) letter (of 11/25/66) . . . I am therefore recommending that NDA 50–028 be approved for certification and the labeling as submitted be approved also."