normalities at birth were found, and examination of the detailed gross findings of skeletal tissues with respect to number of ribs and sternal bone structure and humerus length failed to reveal any difference between the controls and animals receiving graded doses of these antibiotics administered either orally or subcutaneously. A maximum dose of 600 mg./kg./day was employed.

January 13, 1967.—Submission by Bristol of a marketing report for a number of penicillins. This is submitted as support for Bristol's contentions that the incidence of methicillin-resistant staphylococci has not risen despite widespread use of the semi-synthetics. The general utilization of cloxacillin is shown to be comparable to 1) the total penicillin market and 2) that of Bristol's preparations of penicillin G and V.

February 15, 1967.—Comments by Dr. W. E. Dye (FDA) on Bristol's letter of 11/25/66 concerning labeling changes for Tegopen. Dr. Dye offers these remarks: (1 "Expert academic medical opinion continues to support the present labeling for these drugs and to maintain that penicillin G is the drug of choice for the treatment of infections caused by susceptible strains of Gram positive cocci, and that the penicillinase-resistant penicillins should be largely reserved for the treatment of disease caused by penicillinase producing staphylococci. This advise has been obtained from experienced infectious disease experts with well staffed and equipped laboratories . . . Expert medical opinion does, however, concede that '. . . . for initial therapy while awaiting the results of laboratory tests when the presence of resistant staphylococci are suspected . . . a penicillinase resistant penicillin is indicated." Opinion is divided on whether or not to switch to penicillin G or V if subsequent cultures revealed the presence of penicillin G susceptible streptococci, pneumococci or staphylococci. It is known that short periods of therapy with penicillinase-resistant penicillins can induce the formation of penicillinase in certain strains of staphylococci. This means that the staphylococcus isolated prior to penicillinase-resistant penicillin therapy might be penicillin G resistant 24 to 48 hours later when the results of the drug susceptibility testing on the initial isolate become available . . . I know of no instance where this phenomenon has been of clinical importance. 2) There is no doubt that the safety and efficacy of Tegopen . . . has been or can be demonstrated in the dosages recommended for the treatment of infections caused by susceptible strains . . . 3) The emergence of strains of staphylococci resistant to penicillinase-resistant penicillins does not, on the basis of several years of experience, appear to be a significant problem in this country or in England . . . The (existence) of these organisms, however, and their cross resistance wish other penicillins should be incorporated into the new labeling for these antibiotics. 4) If significant changes are made in the labeling of Tegopen, all other manufacturers of penicillinase-resistant penicillins should be notified simultaneously."

February 16, 1967.—Telephone conversation between Dr. H. C. Anderson (FDA) and Dr. H. C. Peltier (Bristol). Dr. Anderson asked whether Bristol would be willing to combine their clinical data with that obtained by the other two producers of dicloxacillin in order to obtain early approval of the Form 5. Dr. Peltier responded that his lawyers were concerned about the possible antitrust aspects of this proposal and that, furthermore, Bristol was anxious to have the application approved at the 125 mg. dose, which had not been investigated by the other companies.

March 17, 1967.—Conference between FDA and representatives of Bristol. Dr. Anderson (FDA) informed the sponsor that our review of clinical data for dicloxacillin 125 mg. capsules and oral suspension indicated that the low dose is effective against upper respiratory infections due to Group A streptococci and against mild soft-tissue infections caused by *Staphylococci Aureus.* The sponsor is to submit a draft package insert covering these indications.

March 21, 1967.—Submission by Bristol of revised package circulars for dicloxacillin. Minor changes are incorporated in this revision. Also included are case reports for 18 patients with staphylococcal infections treated with the low dose of dicloxacillin (125 mg. 4 times daily in adults and 12.5 mg./kg/day or less in children). The sponsor states that bacteriological cure was established in 17 or 18 cases.

March 27, 1967.—Submission by Bristol correcting a minor error in the submission of 3/21/67.

March 28, 1967.—Medical Officer's Review of addendum to Form 5 on use of low doses of dicloxacillin in clinical infections. This report is summarized by Dr. Shurin (FDA) as follows: