

5. Methicillin-resistant strains show variable resistance to the isoxazole penicillins, depending on inoculum size and length of incubation. Dicloxacillin is more effective than oxacillin against a large inoculum and may be useful in treating methicillin-resistant strains.

6. Resistance to dicloxacillin develops in vitro in the same step-wise fashion found for methicillin, oxacillin, and cloxacillin. There is no evidence that the use of dicloxacillin in vivo would be more likely to result in the emergence of resistant strains.

*July 25, 1966.*—Submission by FDA to Bristol of draft monographs to provide for certification of sodium dicloxacillin monohydrate and pharmaceutical dosage forms thereof. In the same letter it is recommended that a more specific quality control procedure for establishing the identity of the 3-(2,6 dichloro-phenyl)-5-methyl-4-isoxazole carbonyl chloride be established.

*July 29, 1966.*—Telephone conversation between Dr. A. E. Smith (FDA) and Dr. H. Feltier (Bristol). Dr. Smith requested that the sponsor make 3 minor changes in the package insert for dicloxacillin.

*July 29, 1966.*—Submission by Bristol of the revised draft labeling incorporating the changed requested by FDA (telephone conversation of 7/29/66). The trade name for the drug is to be changed to "Dynapen".

*August 9, 1966.*—Telephone conversation between Dr. P. J. Weiss (FDA) and Dr. H. Frediani (Bristol). Dr. Frediani stated that 100 gm. of a proposed standard for dicloxacillin and the 5A molecular sieve to be used in proposed tests would be shipped to FDA. Analytical data for the standard would also be sent.

*August 12, 1966.*—Submission by Bristol of a manuscript copy of the layout for a five page announcement advertisement for dicloxacillin. The sponsor points out that this advertisement contains the text of the package circular.

*August 12, 1966.*—Submission by Bristol of proof copy of labels and cartons for dicloxacillin. The sponsor requests that FDA review this material before he proceeds with final printing.

*August 15, 1966.*—Response by Bristol to the proposed dicloxacillin monograph. The following suggestions are offered: 1) That the concentration used in the toxicity test be changed from 20 to 16 mg. to put it in accord with the dosage used on oxacillin and cloxacillin. 2) That the solution used for the pH test be prepared to contain 10 mg. instead of 30 mg. per ml. 3) That a more specific assay for organic chlorine content be used. 4) That the oral preparation of dicloxacillin be referred to in the labeling as a suspension and not a solution.

Bristol states in this submission that it is their intention to market a 62.5 mg. capsule of dicloxacillin in addition to the 125 and 250 mg. preparations. The formula, manufacturing instructions, finished product specifications, label, carton, and insert are included.

*August 17, 1966.*—Letter from FDA to Bristol acknowledging receipt of the proposed dicloxacillin standard, lot #66132. Assay data for the stated potency, the reference used, and the assay data for the infra-red and organic chloride results are requested.

*August 15, 1966.*—Conference between FDA and Bristol. The major subject discussed was the sponsor's claim that Dynapen is effective at a dosage level of 125 mg. given four times daily. It was pointed out that the Form 5 contains data for only 9 adults with penicillin-resistant staphylococcal infections treated at this dose. The sponsor agreed to review their material from this point of view. In addition, the fact that 13 clinical investigators of dicloxacillin have submitted no cases was brought up and an explanation was promised. It was recommended that the statement in the labeling that larger or more frequent doses may be used for more severe infections be changed to read that they should be used.

*August 30, 1966.*—FDA review of Bristol's letter of 8/15/66. The following remarks are made. 1) There are no objections to the proposed change in the pH test. 2) Potency should not be corrected. "If bulk material is sold for manufacture in finished products, the potency 'as is' should be considered." 3) The percent chlorine test should be retained with the additional statement the "the free chloride content must not exceed 0.5%". 4) The toxicity dose should be kept at 20 mg. since this was proposed by Ayerst and, in any case, different doses are used for 2 forms of oxacillin.

*September 6, 1966.*—Submission by Bristol of new package circulars for dicloxacillin incorporating several editorial changes. Also included is Bristol's review of resistant staphylococcal infections treated with the low dose form of dicloxacillin.