grossly, then autopsied for visceral examination and finally examined for skeletal abnormalities. Furthermore it was recommended that all pups be examined.

February 28, 1966.—Memorandum from A. Kirshbaum to R. Norton containing review of proposed regulations for dicloxacillin. The following recommendations are made: 1) A method for percent dicloxacillin in terms of chlorine content should be submitted. 2) Tests for optical rotation and free acid content are possibly desirable but not absolutely necessary. A method for chlorine content is described in detail.

January 27, 1968.—Amendment by Bristol to the Form 5. This contains a revision of the Finished Product Specification with methods for moisture content and pH. The tolerance limits given are moisture—maximum 1% and pH—range 5.0–7.5.

March 25, 1966.—Submision by Bristol of a status report of clinical investigators of dicloxacillin. A total of 469 case reports had been received from 21 investigators at this point.

June 20, 1966.—Conference between FDA and representatives of the sponsor. The following areas were covered: 1) Reproduction studies. Rabbit, mouse and rat studies had been performed. In rabbits, diarrhea had resulted from the initial dose of dicloxacillin causing difficulty in impregnation. In the mouse study stunting and light weight pups had been obtained. The company agreed to repeat this study. In rats there was a question of whether dicloxacillin had decreased fertility. Sections of testes were to be examined but it was unclear whether the ovaries were still available. 2) Toxicity studies. Previous requests by FDA had been satisfied; it was now requested that, since in the 12 week chronic toxicity study autopsy data had been submitted for only a single animal, the information be supplied for the remaining animals. 3) Labeling. It was recommended that the observation that dicloxacillin interfered with the enteric flora of rabbits and inhibited subsequent impregnation be included in the labeling. This would be discussed at a later conference. Dr. Peltier (Bristol) agreed to add to the labeling, statements to the effect that "where sensitivity tests indicated a given staphylococcus was sensitive to Penicillin G, a change to this drug may be considered", that eosinophilia and "occasional but transient SGOT elevations" are adverse reactions to dicloxacillin and that it is advised that "the drug be administered on an empty stomach."

July 1, 1966.—Submission by Bristol of revised package circular incorporating the changes discussed in the conference of 6/20/66 and advising that the trade name "Hypen" has been chosen for dicloxacillin.

July 12, 1966.—Letter from FDA to Bristol advising that, in order to bring the labeling for dicloxacillin into conformity with that of the other penicillinase-resistant, semisynthetic penicillins, the following sentence should appear in capitals or bold face as the beginning of the "Indications" section: "Hypen 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."

July 12, 1966.—Drug Control Review Notes (FDA). It is concluded that controls are inadequate and that the sponsor should be notified as follows: 1) The 3(2,6 dichlorophenyl)-5-methyl--isoxazole carbonyl chloride should have a specific identity test. 2) The Form 5 should be amended to specify that the bulk drug and the finished dosage formulations should conform to the applicable Federal Regulations 3) Extended stability data should be submitted for the bulk drug and for all dosage forms.

July 13, 1966.—Submission by Bristol of new labeling incorporating recommendations made in FDA's letter of 7/12/66 and by telephone. Dr. Peltier (Bristol) adds that "We still feel that . . . such a statement (recommending a switch to another penicillin if the patient's infection is not due to a penicillinase-producing staphylococcus) 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."

July 15, 1966.—Letter from Dr. William M. M. Kirby (Professor of Medicine, University of Washington) to Dr. Barzilai (FDA). Dr. Kirby states that he has discussed with Dr. Peltier the labeling for dicloxacillin. He says that "it occurs to me that the time has arrived when it is appropriate to say that these drugs (the semisynthetic, penicillinase resistant penicillins) are effective in staphylococcal, streptococcal, and pneumococcal infections . . . In vitro, these drugs are appreciably more active against streptococci and pneumococci than they