March 31, 1967.—Submission by Bristol of revised labeling incorporating several minor revisions.

April 26, 1967.—Addendum to medical officer's review stating that cases submitted by Dr. William Abruzzi were not considered for evaluation.

April 26, 1967.—Telephone conversation between Dr. Anderson (FDA) and Dr. Peltier (Bristol). Dr. Anderson advised that FDA would like the statement "This drug should not be prescribed for neonates because safe conditions for use have not been established", added to the labeling and that indications for the drug should be revised to mention that the drug is specifically effective against penicillin G resistant staphylococci, and that the latest stability data on the capsules should be submitted.

April 26, 1967.—Submission by Bristol of stability data on 12 lots of dicloxacillin.

April 27, 1967.—Conference between FDA and Bristol. It was recommended that certain questionable side-effects such as listlessness and tiredness be removed from the labeling.

April 28, 1967.—Telephone conversation between Dr. David Holvey (Bristol) and Dr. P. Shurin (FDA). Dr. Holvey inquired about certain cases which were cited in FDA's medical review. Dr. Shurin supplied him with the case numbers of these cases.

May 1, 1967.—Submission by Bristol confirming the results of conference of 4/27/67.

May 31, 1967.—Conference on current problems in labeling of dicloxacillin. Bristol reiterated the desire to recommend dicloxacillin for infections due to all sensitive Gram-positive cocci. Their position is as follows: (1) In well controlled studies, Bristol has not been able to demonstrate any disadvantage of dicloxacillin, as compared to penicillin G or V in the treatment of streptococcal pharyngitis. (2) The early fear that staphylococci would develop widespread resistance to semi-synthetic penicillins has not been borne out by many years' usage. (3) The contested claims are now permitted for such drugs as novobiocin, tetracycline and triacetyloleandomycin. Therefore, more stringent requirements for dicloxacillin are discriminatory. (4) It is possible though not borne out by any clinical evidence, that an infecting strain of *Staphylococcus* may increase its level of penicillinase production during the course of an infection. In such a case, switching treatment from dicloxacillin to penicillin G following the results of original cultures, would be contraindicated. (5) It is unwarranted to change treatment when the patient is responding well, if there are no real or theoretical disadvantages associated with the original medication. Dr. Hodges (FDA) agreed to take the matter under further consideration.

June 10, 1967.—Drug control review notes state that "a 12 month expiration period could be approved for all potencies of the capsules and for both potencies of the powder for oral suspensions. The stability data for the reconstituted suspension indicate that it would be stable for 7 days at room temperature and for 14 days on ice."

June 13, 1967.—Submission by Bristol informing FDA that the original oral suspension of dicloxacillin has been found to be so bitter as to be unpalatable. The company has, therefore, developed a method of wax coating the drug and claim to have "determined that the drug in this coated form is as readily available as the original formulation." This amendment contains manufacturing instructions, specifications, test methods, stability data, labeling, blood level studies and samples of this formulation.

June 14, 1967.—Letter from FDA to Bristol recommending that the package insert be revised as follows: 1) The listing of the organisms should include "penicillin G resistant and penicillin-G sensitive staphylococci. 2) There should be a statement to the effect that "if it is determined that the infection is not due to the penicillin G resistant staphylococcus, a change to penicillin G or phenethicillin may be considered . . .

June 19, 1967.—Conference called to discuss inclusion of the above statement (item 2, 6/14/67) in the labeling for dicloxacillin. Bristol's position on this has been exhaustively cited above (see notes for 5/31/67, 11/25/66 and 7/20/66). The FDA position remained that widespread use of dicloxacillin and related drugs for various infections due to Gram-positive cocci may lead to their declining usefulness as antistaphyloccal agents and thereby produce a serious public health problem.

June 28, 1967.—Medical Officer's review of data pertaining to the coated form of dicloxacillin for oral suspension. Blood levels and urinary excretion obtained with this preparation were comparable to those obtained with the old formula.