given to salesmen and said to be used as a "keeper"); Exhibit B (copy of memo from Bristol ad department indicating journals in which Dynapen will appear, and ad tear sheets); Exhibit C (a memo from Bristol's General Sales Manager outlining action taken regarding distribution stoppage and copy of telegram to wholesale accounts); and Exhibit D (a memo estimating amount of Dynapen shipped into hospital and retail accounts).

Dr. Ley handed out copies of an FDA-prepared guideline to proper indications for Dynapen, which he proposed as the "core" of the remedial letter. He said the main thrust of the letter should be on these indications, and that other complaints about the initial promotional letter were of lesser importance and therefore not necessary to include.

Mr. Simenton then said he understood that the guideline plus opening and closing paragraphs would comprise the letter. Drs. Ley and McCleery commented that it would be appropriate to use the guideline and to return Monday June 3 with a second draft.

The discussion turned to details in the FDA guideline. Dr. Peltier claimed that the wording relating to "250 mg q. 6h" in the draft was not in accord with the package insert. Dr. Ley indicated that this and other points were open to discussion.

Next, the portion of the guideline dealing with the problem of staphylococcal resistance to the methicillin-family, including Dynapen, was discussed at length. This was led off when Mr. Simonton and Dr. Peltier asked about the scientific basis for the letter's emphasis on the appearance around the world, and recently in the U.S., of resistance to this class of antibiotics.

Dr. Peltier said (as he had said previously) that development of resistance during the therapy of a single patient was a minor problem. But Dr. McCleery interrupted and said it was contrary to reason to mix the two subjects. He agreed that the development of resistance during therapy is a minor problem, but said that the major problem is the increasing frequency of appearance in hospitals resistant strains of organisms of the microbial population in point.

Drs. Ley and Minchew supported this. Dr. Ley said there is good evidence to demonstrate that the widespread use of methicillin has been accompanied by the development of resistant strains. He said this has been the experience with all antibiotics in wide use (hospitals, etc.), but that proof of association beyond reasonable doubt has not been obtained, not even with penicillin G. It was also emphasized that the development of resistance to penicillin G by staphylococci does not occur by a particular strain during treatment of a single patient. However, presumably "genetic-environmental-selection" of penicillin-G resistant staphylococci has led to the prevalence of this problem. It was therefore reemphasized to Dr. Peltier that the problem of a particular strain of staphylococcus developing resistance during therapy of a given patient is separate from the development and propagation of resistant strains among the microbial population as a whole and should not be equated.

Mr. Simonton said that he wanted Bristol to have the information that FDA had collected.

Dr. McCleery said he would give the references and said the record would show the information was supplied. He gave these references:

1. "The Resistance of Staphylococci to Penicillins and Cephalosphorins," a paper by F. H. Kayser, Institute of Medical Microbiology, University of Zurich, Switzerland, given June 26, 1967 at the 5th International Congress of Chemotherapy, Vienna, Austria (6/26–7/1, 1967)
2. "Methicillin-resistant Straphylococci in a General Hospital," E. W. Calley, et. al., *The Lancet*, 13 March 1965.
3. "A screening test for the detection of methicillin-resistant organisms," G. M. Churcher, Department of Pathology, Plymouth General Hospital, Plymouth, England, *J. Clin. Path.* (1968) 21, 213–217.
4. "Resistance to cloxacillin among hospital staphylococci," G. C. Turner and P. E. Cox, Department of Pathology, Sefton General Hospital, Liverpool, England, *J. Clin. Path.* (1967) 870–874.
5. "Antibiotic Susceptibility of Staphylococcus aureus isolated from cases of Bacteraemia in Denmark 1957–66," O. Jessen *et. al.*, an abstract (page 799 of proceedings, B 1–17) of presentation at 5th International Congress on Chemotherapy (see item 1 above).
6. "Combination Therapy of Infections Cause by Methicillin-Resistant Staphylococci with Rifampicin plus Pucidic Acid or Novobiocin," Klaus Jensen, an abstract (pages 783–784 of proceedings, A 1–6/19) of presentation at 5th International Congress of Chemotherapy (see item 1 above).