APPENDIX IV

DOCUMENTS ON VIBRAMYCIN (DOXYCYCLINE) FROM FDA FILES

Labeling for "Vibramycin" (doxycycline HC1, Chas. Pfizer & Co. NDA 50-007)

JUNE 29, 1967.

ROBERT M. HODGES, M.D.,
Director, Office of New Drugs.
Dr. ALAN E. SMITH,
Acting Deputy Director, Division of Anti-infective Drugs.
JOHN M. DAVITT,
Pharmacologist, Division of Anti-infective Drugs.

As requested, here are the statements proposed by DAD pharmacologists for inclusion in appropriate sections of Pfizer's labeling for Vibramycin:

1. At relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.
2. As with some of the other tetracycline antibiotics, gross discoloration of the thyroids, ranging in intensity from brown to black, can be produced by high oral doses of Vibramycin in several species of experimental animals. The significance of these changes is uncertain. I^{131} uptake studies in rats and dogs failed to demonstrate any interference with thyroid function.

The Pfizer people maintain the first statement is superfluous since both GI disturbances and evidence of hepatic effects in humans are already mentioned in the labeling.

Although they agree that the second statement is factual and belongs in the labeling, they object to its use at this time on the grounds that it would result in an unfair competitive disadvantage for their product. They have indicated willingness to include this statement in their labeling only when competitive products are similarly labelled.

JULY 31, 1967.

NDA 50-006, 50-007

MEMORANDUMS OF CONFERENCE AND TELEPHONE CONVERSATION

CONFERENCE

Present: Dr. Monroe Trout, Chas. Pfizer & Co., Inc.; Mr. Joseph P. Aterno, New York, N.Y.; and Dr. Herbert L. Ley; Dr. Edwin I. Goldenthal; Dr. Alan E. Smith; Dr. Kent Potts, FDA; Mr. Julius Hauser; Mr. Ola Bain.

Subject: Vibramycin (doxycycline) NDA 50-006 and 50-007.

Proposed changes in the label and labeling for Vibramycin as outlined in the Memo of Conference of July 28, 1967 were reviewed in detail. The Pfizer representatives objected to any changes because the requests were being made too late, they thought final agreement had previously been reached, they have already printed many package inserts and containers. Dr. Ley pointed out that antibiotics are unique in that the Commissioner, not the Bureau of Medicine, has the final judgment regarding their approval. Hence a company takes a risk if printing is started before approval of the Commissioner is granted.

Discussion proceeded to the specific changes which had been recommended. In the labeling under "Action" we had suggested that the sentence about in vitro antibacterial activity be omitted or followed by the statement: "This is of no known clinical significance". Pfizer objected as they believe this degrades the importance of in vitro sensitivity testing. Dr. Ley said he would prefer that they omit the whole thing as the differences noted were so small that we believe they are of no consequence. Other suggested changes in the package insert were considered minor by Pfizer and they voiced no specific objections.

With regard to the immediate label and carton changes the visitors strongly objected as they are using the same format for Vibramycin that they have previously used for other tetracycline products, they don't see how all the requested information can be included on the front panel, they have already printed a number of these pieces and it would be expensive and time-consuming to have them redone.

After considering all facts presented Dr. Ley offered the following suggestions:

1. The company could use their present supply of immediate labels and cartons