McNEIL

REGULATORY AFFAIRS
McNEIL LABORATORIES, INC.

No. 988

17 July 1973

TO:

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FROM: PHSeay

RE: TYLENOL-500

On 10 and 11 July, I discussed the status of TYLENOL-500 with Dr. Dassler, Mr. Crabbs and Mr. Purvis.

I reviewed the status of TYLENOL-500 capsules and pointed out the difficulty that FDA approval of the TYLENOL-500 capsules for OTC use has caused. We had recommended this product be approved R_X - this recommendation was based on the CFR statement on acetaminophen tablets OTC (325 mg. tablets; 2600 mg. maximum daily dose). The 500 mg. capsules cost about 2 1/2 times as much as 500 mg. tablets to produce. If we market the capsules OTC and other companies come into the market with 500 mg. tablets, we could not compete. Dr. Dassler said that other companies could not do this as they would be required to furnish the same information that we have provided in our NDA. I agreed with her that they should but I have had a continuing dialogue with Mr. Byers in compliance about the fact that there are acetaminophen products in the market without approved NDAs - i.e. 500 mg. acetaminophen plus butabarbital, 650 mg. tablets of acetaminophen, and numerous suppositories. Dr. Dassler indicated that compliance is checking on these products and they will take action soon. [Mr. Byers has told me previously that he could not take action until the review was completed. This is likely to take 9 to 12 months.]

I discussed with Dr. Dassler, Mr. Crabbs and Mr. Purvis the requirement and proper procedure for changing from the capsule to a tablet. The tablet will contain 500 mg. of acetaminophen and have the same formulation as the present 325 mg. tablet - it will simply be larger. Dr. Dassler said that from the medical standpoint a study on bioavailability would be required. She suggested that we discuss the protocol for that study with Dr. Murdock. Data on Chemistry and Controls should be discussed with Mrs. Postman. There was much discussion on the proper procedure for carrying out the study and submission. It was agreed that the best procedure was to carry out the study on bioavailability without any submission to an IND. Submit the OTC labeling for TYLENOL-500 capsules - and obtain approval. Then submit an NDA on TYLENOL-500 tablets. The NDA would consist of the section on Manufacturing and Controls, bioavailability (equivalence of 500 mg. tablets to 500 mg. capsules) and referral to the approved NDA on TYLENOL-500 capsules.

There is some question regarding the total daily dose that will be approved OTC. The present CFR statement limits the total daily dose OTC to 2600 mg. (eight 325 mg. tablets). Our studies on TYLENOL-500 capsules were carried out at 4000 mg./day. During the second meeting of the OTC panel on internal analgesics, the panel stated (1)"....., recent studies indicate that 600 mg. doses of aspirin, phenacetin, and acetaminophen are equipotent." and (2) for aspirin: "Usual adult dose not more than 2 tablets every 4 hours for 24 hours." (see attached). These statements taken together indicate a maximum daily dose of 3900 mg. [It may be desirable to suggest to the OTC panel that the upper dosage level be set at 4000 mg./day. The next meeting of this panel is 30 July 1973.]

It appears that Lilly has filed a supplemental application for a combination of acetaminophen 650 mg. and 65 mg. of propoxyphene.

It appears that Dr. Prescott-Smith has reported that a report exists indicating that 6 gm. of acetaminophen produced hepatic and renal problems.

Interest has also been expressed in modifying the acetaminophen molecule to avoid hepatic damage.

P. H. Seay

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Att: