being given for the Upjohn product. Subjects receiving a double dose (priming dose) would be expected to yield higher blood levels. The priming dose is recommended in the Upjohn enclosure because of the unrealibility of the enteric-coated tablet. The Abbott Erythrocin® Stearate Filmtab® is not an enteric-coated tablet. Hence, like the erythromycin ethylsuccinate granules, it will give earlier peak blood levels than will the E–mycin enteric-coated tablet. Erythromycin stearate is not as susceptible to acid destruction as is erythromycin base. Because of this fact and our formulation techniques, the Abbott tablet does not need to be enteric coated.

Comparative bioavailability studies should be done using the same dose under similar study conditions. Bioavailability studies are not the same as clinical studies and the comparison of products at their clinical doses implies that the products with the highest doses are clinically the most efficacious. The need for a "priming" dose with the E–mycin tablet is stated in the 1974 *Physicians' Desk Reference* (PDR), product information section:

"Adults: 250 mg. four times daily is the usual dose. An initial dose of 500 mg. is suggested to assure adequate and significant blood levels from the first dose and to eliminate variability of absorption which is sometimes associated with enteric coated preparations."

The priming dose represents extra medication costs to the patient. A bioavailability study conducted in our laboratories showed enteric coated E–mycin tablets have erratic absorption and 7 of 22 subjects (or about one-third) had no measurable drug levels for the first six hours. When bioavailability information is presented as average values, it masks the individuals differences and subjects with no levels are not apparent. This study does not indicate what range of values make up these average values or if there were individual subjects with unmeasurable blood levels.

The protocol used in CS #056 was designed for an enteric coated product, so the serum level curve of Erythrocin Filmtab was inadequate characterized. Erythrocin Filmtab usually will achieve peak serum levels one to two hours earlier than enteric coated E–mycin tablets. Serum samples were not collected where Erythrocin Filmtab normally achieves its peak serum levels. As discussed under CS #037, the blood level curve for the Abbott tablet is not properly characterized under these conditions.

SUMMARY

When bioavailability information is provided in this pseudotechnical manner, it is not fully recognized as advertisement. The studies can be designed to be technically biased. This is clearly shown when one compares CS #037 and CS #056. The comparison in CS #037 was not done at recommended doses, so the Abbott suspension (granules) appeared to yield inferior drug serum levels. In CS #056, the reader may be unaware of the erratic drug absorption characteristic of the E–mycin tablet. In this study, tablets with different availability characteristics and different reliability (enteric versus non-enteric tablets) were tested at different dosing intervals (every six hours and every twelve hours) and with and without priming doses (E–mycin and Erythrocin). The study was designed to catch the peak heights for E–mycin and to miss the peak heights for Erythrocin. Given these variables, we do not feel that this study is a valid comparison of anything except differences between E–mycin when dosed every six hours versus every twelve hours.

Since Abbott studies do not employ the extra priming doses, we have no laboratory data that would be comparable to the Upjohn study. However, in studies where we have given 500 mg. of erythromycin stearate in a single dose (as part of a twice daily administration schedule), we have obtained average peak levels ranging from 1.1 to 1.9 mcg./ml. (mean of four studies, 1.57). This can roughly be compared to the first 500 mg. dose of E–mycin given in Treatment B. There E–mycin gave an average peak level of 1.04, before the second dose was given at six hours.

We are enclosing a copy of the previously cited article which explains some of the liabilities of bioavailability information in greater technical detail.

Bioavailability studies must be viewed as only one segment of the total product performance pattern. A bioavailability evaluation is a single study of one product lot. To the patient, clinical efficacy studies, quality assurance, stability, development and packaging programs must each function to achieve a quality drug product. Recent actions by the F.D.A. suggest that greater regulatory awareness and emphasis will be placed on these latter product programs.