

11816 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

The main point that we wish to make is that Upjohn is using bioavailability studies for promotional purposes. To do this they are designing their bioavailability studies to be biased in favor of their product and negatively biased toward competitive products. Certainly, we feel this is a prostitution of the science of bioavailability and does little credit to scientists who allow such distortion to occur. Such use of bioavailability data tends only to create confusion in the minds of the hospital and retail pharmacists, who are usually not sufficiently knowledgeable of the science of bioavailability to detect the effect of these protocol designs. The pharmacist is unduly influenced by studies that he does not realize were improperly conducted. The Upjohn studies consistently insert this protocol design bias in favor of their product and no acknowledgment of this bias is ever given in the study. We know it is highly unlikely that the pharmacist will recognize these subtle biases nor will he go to the trouble to determine for himself whether such bias does exist. Since the Upjohn studies are consistently done with these built-in biases it is obvious it is not accidental or unintentional. We consider this action of Upjohn unscientific and unconscionable. A few specific comments on each study follow:

STUDY CS NO. 050

In this protocol the dosing schedule is at fault. This is a more subtle difference than seen with some of the earlier studies that were analyzed. The time at which the dose is given in relation to meals does influence the blood levels of erythromycin that are obtained. Our product literature recognizes that erythromycin stearate gives optimum blood levels when taken before meals and we do not recommend any dosing after meals. Our product enclosure for Erythrocin® Stearate Filmtab® states, "Optimum blood levels are obtained when doses are given on an empty stomach." Our experience has shown that Erythrocin Stearate Filmtab gives optimum serum levels when the product is taken one or two hours before meals. Serum levels of E-Mycin (erythromycin base) are substantially altered, depending on whether the drug is given one or two hours before meals. This is obviously why the E-Mycin dosage recommendation in the 1974 *Physicians' Desk Reference* is, "E-Mycin is well absorbed when given orally immediately after meals or between meals on an empty stomach." This direction does not indicate that E-Mycin should be taken at least two hours before meals to obtain optimum levels but is perhaps covered by the "between meals" indication.

The enclosed studies show this difference. These studies compare the E-Mycin to Abbott Erythromycin Base Filmtab Tablets. Study #72-9 shows the effect of giving both products two hours before meals. Comparable levels are obtained. Study #72-82 shows the effect giving the same medication an hour before meals. In this case, the E-Mycin levels are significantly reduced. This simply illustrates that the protocol design can be expected to influence the outcome of the study results. Note also that our studies compare two different dosage forms (tablets, Abbott vs. enteric tablets, Upjohn) of the same chemical entity, not different chemical entities (erythromycin stearate vs. erythromycin base) as does Study CS#050. We feel the former comparison is more valid than the latter, since each chemical has different dissolution patterns, absorption characteristics, gastric resistance, etc. Our previous comments pointed out the short-comings of enteric-coated tablets (E-Mycin, Upjohn).

As we previously stated, when bioavailability data are presented as average values, it effectively masks the results of individual subjects. Therefore, subjects with no levels are not apparent nor is the deviation from the average value apparent. It is for this reason that we believe that average values should be given along with the standard deviation. Data on the number of subjects that had no measureable blood levels at any of the sample periods should also be mentioned. Note that this information is provided in our Studies #72-9 and #72-82. For further discussion of this, refer to the paper by Drs. Chun and Seitz that was included in our first submission. E-Mycin, because of its enteric coating, does have an unusual drug absorption pattern. It is for this reason that the dosage administration is restricted to immediately after meals or between meals on an empty stomach.

STUDY CS NO. 071

The problem with this study should now be quite obvious. This protocol calls for Erythrocin® Stearate Filmtab® to be administered immediately after meals. As we have previously pointed out, this is absolutely contrary to our recommended dosage schedule. It would be expected that erythromycin stearate would