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April 5, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket # 2005D-0030 to RES # cd03168

Dear Madam/Sir:

I have been asked to comment on the Draft Guidance for Industry on Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling: Availability. My comments are as follows:

1. There is a common misperception that the breast functions kinetically much like the urinary bladder and this underlies such recommendations as “pump and dump” (lines 593-596). In fact, it is important to emphasize in your guidance that drug concentrations in breast milk are generally in a bi-directional dynamic equilibrium with maternal plasma concentrations. Therefore, a general principle is that one way to minimize infant exposure to all drugs is to nurse just before the next drug dose is administered. This also means that fetal exposure is not related to mAUC as much as to the actual plasma, and therefore milk, concentration at the time of breast feeding. This also argues against pooling milk samples as this discards information that is relevant to analyzing kinetics of drug transfer into milk.
2. A related concern is that special attention needs to be given to drugs that exhibit nonlinearity in maternal protein binding within the range of plasma concentrations obtained during therapy. Prednisolone is an example of such a drug (see: Greenberger PA, Odeh YK, Fredriksen MC, Atkinson AJ Jr. Pharmacokinetics of prednisolone transfer to breast milk. Clin Pharmacol Ther 1993;53:324-8.).

2005D-0030

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3. Regarding lines 218-220, it needs to be pointed out that just measuring plasma levels in infants only defines V/F and CL/F because the absolute bioavailability is not known.
4. Regarding line 28 and subsequent lines 88-93, I am not aware that lactation *per se* exerts significant effects on maternal pharmacokinetics and feel that the emphasis on lactation in these sections is perhaps misdirected. What is probable is that maternal pharmacokinetic changes that occur during pregnancy persist for a variable period in the postpartum state, regardless of whether the mother is breast feeding or not. Therefore, I believe that these maternal changes are best addressed by serial studies during pregnancy and the postpartum state (see: Frederiksen MC, Ruo TI, Chow MJ, Atkinson AJ Jr. Theophylline pharmacokinetics in pregnancy. Clin Pharmacol Ther 1986;40:321-8.).
5. As far as the sequence of recommended studies is concerned, I would favor listing the studies in order of increasing complexity. In other words, maternal milk only, maternal plasma + milk, maternal plasma + milk + infant plasma.

I hope that these comments are helpful.

Sincerely yours,



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cc: Kathleen Uhl, M.D..