

April 11, 2005  
Division of Dockets Management HFA-305  
Food and Drug Administration  
5630 Fishers Lane Room 1061  
Rockville, MD 20857

Re: Docket No. 2005D-0030 (Draft Guidance for Industry on Clinical Lactation Studies)

Dear Madam/Sir:

We are pleased that FDA is focusing on lactation studies as part of the drug approval process. This research has the potential to become an important source of useful information for breast-feeding women. Currently, information in the label under the heading "Nursing Mothers" is rarely helpful. For example, the current labels state:

"Sumatriptan is excreted in breast milk. Therefore, caution should be exercised when considering the administration of sumatriptan to a nursing woman."

or

"The estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. . . . Nevertheless, caution should be exercised when digoxin is administered to a nursing woman."

or

"It is not known whether this drug [Plavix ] is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the nursing woman."

These examples are indicative of the current lack of guidance available to nursing women.

In the new edition of our book *Worst Pills, Best Pills*,<sup>1</sup> we made an effort to improve upon these summary statements by focusing on what was present elsewhere in the drug's label. We provided our readers with data from human lactation studies (where they had been done); where information was lacking, we based our advice on a combination of the label's preclinical (animal) and clinical data. These data included an analysis of adverse effects from animal studies (chronic toxicity, reproductive toxicity, carcinogenicity, and genotoxicity), as well as human adverse events. An approach of this kind represents an interim solution until human lactation data are more widely available.

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<sup>1</sup> Wolfe SM, Sasich LD, Lurie P et al. *Worst Pills Best Pills*, Pocket Books, NY, 2005.

For example, the label for sumatriptan has the following information on adverse effects to young pups who are exposed at the end of gestation through nursing:

**Sumatriptan Label:**

*“Pup Deaths:* Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1,000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 10 times the maximum single recommended human oral dose of 100 mg on a mg/m<sup>2</sup> basis.”

**Worst Pills Best Pills Advice** (for the triptan group of drugs based on lethality in rat pups derived from labels):

“The triptans have been shown to be excreted in high levels in rat and/or human milk. Because of the potential for serious adverse effects in nursing infants, you should not take these drugs while nursing.”

Physicians and patients look for succinct summaries of lactation information. This should take the form of a summary of all the available information and a simple system analagous to that used for pregnancy (A, B, C, D, X).

Information on the levels of drugs in milk, the impact of the drugs on the fetus, and the impact of pregnancy on internal drug levels is so vital that FDA should make lactation studies a requirement for drug approval. Moreover, the designs of such studies should, as far as possible, be the subject of regulation, not just a guidance. Such studies should be done for all drugs with exceptions to be made only for specific cases where there is no reasonable possibility of use in women of reproductive age, e.g., male-specific disease.

As in other guidances, animal toxicity studies should be performed before any human trials. The FDA’s recent draft guidance, “Guidance for Industry concerning Pharmacokinetics in Pregnancy” makes this precise argument; pharmacokinetic studies are allowed “if the following conditions are met:

- Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data on assessing potential risk to pregnant women and fetuses; and

- The risk to the fetus is not greater than minimal . . .”<sup>2</sup>

### **I. Animal Models**

The Guidelines, as written, do not provide a safety basis from animal data as in the Pregnancy Guidance above. A model for preclinical studies of reproductive toxicity has already been provided by industry in their Segment III studies in New Drug Applications (NDAs); examples of some of these studies include studies from Pfizer and Parke-Davis.<sup>3,4</sup> Steady state dosing with collection of plasma and milk from dams along with plasma levels in pups would show whether and how much drug is transferred and at what rate. Using a radiolabeled drug would permit one to measure parent drug as well as metabolites in plasma (mother and pup) and milk. Rat models for studies on postnatal development include monitoring the offspring with a battery of functional and developmental studies.

### **II. Lactating women who are not breast-feeding**

This group should precede mother-infant pairs as the first type of human study done (Section IVA and B of guidance). One should compare plasma and milk levels as a function of time after steady state dosing with enough women to take into account individual variation in metabolism. Even when the parent drug does not accumulate over time, it may induce changes in metabolism and metabolites that do and so all studies should require multiple dosing.

As pointed out in the Lactation Draft Guidance under “Study Participants”, many maternal factors can affect both lactation and the pharmacokinetics of a drug, including ethnicity, age, general health, weight, diet, smoking, alcohol intake, exercise, and concomitant medications. Studies need assess of these factors and be large enough to provide a general idea of how they might affect drug excretion into milk.

### **III. Studies on mother-infant pairs**

Studies on mother-infant pairs should be done on drugs that have first been tested in I and II above. Information from a drug’s use in the pediatric population can not supplant the need for further lactation studies since much of the pediatric information is anecdotal and/or comes from case reports; there is no comparison with that obtained from a well-conducted study where drug levels are measured and infants carefully monitored. Furthermore, little information is available for the neonate and young infant whose detoxification mechanisms are immature.<sup>5</sup>

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<sup>2</sup> Guidance for Industry concerning Pharmacokinetics in Pregnancy  
<http://www.fda.gov/cder/guidance/5917dft.htm>

<sup>3</sup> Weisenburger WP, Hagler AR, Tassinari MS. Pre- and postnatal development studies of lasofoxifene, a selective estrogen receptor modulator (SERM), in Sprague-Dawley rats. *Birth Defects Res B Dev Reprod Toxicol* 2004;71:171-84.

<sup>4</sup> Henck JW, Craft WR, Black A et al. Pre- and postnatal development of the HMG-CoA reductase inhibitor atorvastatin in rats. *Toxicol Sci.* 1998;41:88-99.

<sup>5</sup> Moore TJ, Weiss SR, Kaplan S, et al. Reported adverse events in infants and children under 2 years of age. <http://www.pediatrics.org/cgi/content/full/110/5/e53>; accessed February 24, 2003.

#### IV. Other Issues

A. Ethical Issues: There are ethical issues to be considered that should be added to this document, including IRB review and informed consent for all participating mothers.

B. Very toxic drugs: In cases where the mother must take very toxic drugs, e.g., immunosuppressive and cytotoxic drugs for cancer chemotherapy, the mother should not breast-feed.<sup>6</sup> In these cases, the risks of severe toxicity or carcinogenicity outweigh the benefits.

There is little argument that breast-feeding is of great value for mother and child, as outlined in the Background of the Guidance, and if a mother needs to take a drug for her own health reasons, she should certainly do so. However, after that decision, the guiding principle should be to do no harm to her infant: if a drug has the potential to harm a nursing infant, the mother should be informed of those harms, both long and short term, and base her decision on whether to nurse on all information available. Much current advice ignores or downplays toxicity,<sup>7</sup> even information available in the drug's label, as if breast-feeding per se were the overarching consideration to be done at almost any cost to the future health of the child. Hopefully, lactation studies (both preclinical and clinical) will provide badly needed data on this important subject. Meanwhile, FDA should make fuller use information already available.

Sincerely,

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Research Analyst

Peter Lurie, MD, MPH  
Deputy Director

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<sup>6</sup> World Health Organization. Breastfeeding and maternal medication.  
<http://whqlibdoc.who.int/hq/2002/55732.pdf>

<sup>7</sup> Ito S. Drug therapy for breast-feeding women. *New England Journal of Medicine* 2000;343:118-126.

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