MEMORANDUM

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To: Pediatric Advisory Committee Members and Invited Experts

Subject: Submitted Public Comments and Evolution of the Draft Guidance for Industry: Clinical Lactation Studies

The Draft Guidance on Clinical Lactation Studies was published in February 2005 and started the clearance process through FDA, HHS, and OMB many months prior. As the Maternal Health Team reviewed the Draft Guidance and comments on the Guidance submitted to the public docket, it became apparent that the background section and other sections of the Guidance needed updating based on more recent data. In addition, the comments pointed out areas where the Guidance was clear and helpful and areas where information in the document lacked clarity or was inconsistent or ambiguous. Based on this feedback, we have considered ways to restructure and reorder some of the information in the document. In addition, we have added some new information. While this memo does not represent official changes to the Draft Guidance document, it presents some of the new information and organization we think should be part of the advice we offer industry on the subject of clinical lactation studies.

1. Background Information on Breastfeeding and the Use of Medicines During Breastfeeding

Many women use medications while breastfeeding, either chronically to treat an ongoing condition or temporarily to treat an infection or relieve symptoms. Surveys conducted in various countries indicate that 90-99 percent of nursing mothers receive a medication during the first week postpartum; 17-25 percent of nursing mothers use a medication by four months
postpartum; and five percent of nursing mothers receive long-term drug therapy (Bennett 1988). For most drugs, there is little or no scientific information about the amount of drug in breast milk, the effects on milk production, the effects of the drug on the breastfed infant, or whether dose adjustment is needed to safely and effectively treat a lactating woman. Therefore, breastfeeding women and their health care providers make decisions about drug treatment and about continuation of breastfeeding during therapy in the absence of data. To take needed drug therapy, a mother may stop breastfeeding unnecessarily, thereby sacrificing the benefits of breastfeeding for her and her infant. Clinical lactation studies can provide much needed data on which to base breastfeeding and treatment decisions.

**Why breastfeeding when medicine is needed?**

Breast milk is the most complete form of nutrition for infants and offers a range of health benefits for breastfeeding women and infants. Research in developed and developing countries, provides strong evidence that human milk feeding decreases the incidence and/or severity of a wide range of infectious diseases including bacterial meningitis, bacteremia, diarrhea, respiratory tract infection, necrotizing enterocolitis, otitis media, urinary tract infection, and late-onset sepsis in preterm infants. Studies suggest that breastfeeding significantly reduces postneonatal infant mortality and rates of sudden infant death syndrome (SIDS) in the first year of life. In addition, data suggest that older children who were breastfed have slightly enhanced cognitive performance and decreased rates of asthma, obesity and overweight, diabetes mellitus (insulin and non-insulin dependent), lymphoma, leukemia, and Hodgkin disease. Maternal benefits of breastfeeding include reduction in postpartum bleeding, earlier return to pre-pregnancy weight, reduced risk of premenopausal breast cancer, and reduced risk of osteoporosis (U.S. Department of Health and Human Services (DHHS) 2000).

The DHHS sponsored Healthy People 2010 Initiative includes the *HHS Blueprint for Action on Breastfeeding*. Goals include increasing the percentage of mothers breastfeeding in the immediate postpartum period to 75 percent and the percentages of mothers breastfeeding at six and 12 months to 50 and 25 percent respectively. (DHHS Services 2000). Data obtained from the CDC National Immunization Survey for years 2000 - 2004, suggest that about 73.8% of American women initiate breastfeeding in the initial postpartum period. About 41% of babies receive at least some breast milk up until three months of age but only 31% are exclusively breastfed. By six months of age, only 21% of infants receive some breast milk and only 11% are exclusively breastfed. The American Academy of Pediatrics (AAP) recommends that all new mothers who are able should breastfeed until the child reaches one year of age. The AAP considers breastfeeding to be the ideal method of feeding and nurturing infants (AAP Section on Breastfeeding 2005). The AAP and its Committee on Drugs issues consensus documents that collate and summarize the limited amounts of data available on the presence of drugs and other chemicals in breast milk (AAP 1989, 1994; AAP Committee on Drugs 2001).

**Transfer of drugs into human milk**

Many, but not all, maternal drugs transfer to breast milk, but the presence of a drug in breast milk does not necessarily indicate a health risk for the breastfed child. Transport of medicines

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into human milk is largely a function of their physico-chemical structures and the concentration in maternal plasma. Factors that tend to produce higher breast milk levels of drug include:
higher maternal plasma concentration, higher lipid solubility, higher pKa, lower protein binding, and lower molecular weight. Most drugs simply diffuse between the two compartments and are driven by equilibrium forces, although a few drugs enter milk by active transport. Drugs that are more lipid soluble may be sequestered in the lipid fraction of the milk and lead to higher concentrations of drug in breast milk than in plasma. Sometimes it is useful to know the actual fat content of milk, which is measured as a creamatocrit.

The pH of human milk is 7.2, about 0.2 units lower than that of plasma. This difference influences the transfer of drugs into milk, more so for drugs that are weak bases with pK\(_a\) values in that range. Rampono et al (2000) demonstrated that the pH of mature milk is remarkably stable (mean ± SD = 7.23 ± 0.27), but studies by Allen et al (1991) suggested that milk pH can be lower in early lactation. Routine milk pH measurement is probably not necessary. However, if milk pH is measured, it should be measured immediately after sample collection because of rapid loss of carbon dioxide.

**Drug bioavailability: mother and infant**

Bioavailability of a medication generally refers to the amount of medication that passes into the portal circulation and bypasses the liver to attain plasma levels. Drugs used orally by the mother that are not orally bioavailable do not attain measurable levels in breast milk. In addition, some topical medications that are used over minimal surface areas or that are not well absorbed transcutaneously may not achieve significant maternal serum levels. Medications administered to a mother that do not attain clinically relevant maternal plasma levels are of minimal risk to a breastfeeding infant and do not require clinical lactation studies. These drugs include products such as: oral vancomycin, inhaled steroids or bronchodilators. Some products applied topically to large surface areas or applied locally to the vaginal or rectal mucosa may achieve significant serum levels.

Some drugs, including therapeutic biologics, ingested from breast milk may not be orally bioavailable in an infant. However, some of these drugs may cause local adverse events in the gastrointestinal tract such as diarrhea, constipation, or gastrointestinal bleeding. Maternal antibiotic use sometimes induces diarrhea in breastfeeding infants. Neonatal bioavailability of drugs is not well understood for a large number of drugs.

**Pharmacokinetics, lactation, and breast milk**

Data on pharmacokinetics during pregnancy and the immediate postpartum period are not available for most drugs, so most clinicians treat lactating women with the same dose studied in and recommended for nonpregnant adults. The physiological changes of pregnancy can be associated with significant changes in protein binding, \(C_{\text{max}}\), and AUC, which can impact drug efficacy and safety. Previously conducted studies that reported drug levels in maternal plasma and breast milk often did not report customary PK parameters (e.g., clearance, half-life). Most

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studies did not account for pregnancy-related changes in plasma protein concentrations and unbound drug in plasma. During the immediate postpartum period, maternal physiology and drug pharmacokinetics transition between pregnant and non-pregnant states. This can contribute to data variability in lactation studies conducted during the first four to six weeks postpartum. (Fleishaker 1989). After the immediate postpartum period, pharmacokinetics in lactating women fall within the range for the population of non-lactating women.

2. **Ethical Research in Mothers and Infants**

Lactation studies are clinical investigations, and therefore, lactating infants enrolled in these studies are protected by 21 CFR 50, Subpart D, the portion of the Protection of Human Subjects regulations that provides additional protections for children involved as subjects in research. Breastfeeding offers many well-documented health benefits to the infant and mother, but non-therapeutic exposure to a maternal drug may expose the breastfeeding infant to unnecessary risk. It is important to consider the expected level of risk to the breastfeeding infant and how this risk compares to the risks associated with the daily activities of a normal, healthy infant at a particular age. Subpart D describes four specific levels of risk for clinical research on children:

1) Research not involving greater than minimal risk.

2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

3) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition.

4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Risk/benefit assessments for drug exposures through breast milk require that a clinician weigh the potential risks of infant drug exposure through breast milk against the known benefits of human milk feeding. Breastfeeding usually does not expose the infant to a new drug. Most often, infants were exposed to the same drug(s) in-utero in significantly higher amounts than that obtained through breast milk. However, there are some situations where an infant does get exposed to a new drug through breast milk. For example, some mothers use nonsteroidal anti-inflammatory agents and/or opiates to treat post-episiotomy or post-caesarean section pain during the postpartum period. When a lactating woman requires new drug treatment for either an acute illness (like an infection or migraine) or a new onset chronic condition, the healthcare team and the mother should reassess the potential risks and benefits of continued breastfeeding based on: known information about the drug, the expected length of treatment, the infant’s age and health, and other relevant factors.

When assessing the ethical issues involved in clinical lactation studies, it is important to distinguish between drug administration to a lactating woman for treatment of her own medical condition and drug administration solely for the purpose of studying maternal and infant effects
of the drug (i.e., the lactating woman is a "healthy" volunteer). Each of the following situations raises unique ethical considerations when considering risk to the breastfeeding infant:

**Lactating women continuing drug treatment for a maternal condition or beginning a new drug treatment for a maternal condition**

Many women with chronic medical conditions continue required drug treatment throughout pregnancy. Their fetuses are exposed to much higher transplacental doses of maternal medication during gestation than they will experience as breastfeeding infants following delivery if their mothers choose to breastfeed. In these situations, the benefits of breastfeeding may often outweigh the risks of continued lower dose exposure to a drug that the infant was exposed to during gestation.

The decision to begin new drug treatment for a maternal clinical indication is a difficult one for any lactating woman who wants to continue breastfeeding her infant. In addition to the risks and potential benefits to herself of starting the necessary medication, the lactating woman needs to consider the risks to her breastfeeding infant. These risks include the possibility of drug exposure through breast milk, as well as the risks of discontinuing breastfeeding in light of the known benefits to the infant. One of the important reasons for performing clinical lactation studies is to provide better information on which to make these difficult judgments of risk and potential benefit. There may be alternative treatments available with a lower documented transmission into breast milk or a better safety profile based on existing neonatal and/or pediatric studies (including juvenile animal models). After a lactating woman begins a clinically indicated medication for the treatment of a maternal condition, it is reasonable to approach her about the possibility of participating in a clinical lactation study of that medication. However, given the health benefit of breastfeeding for an infant, the decision to enroll in a clinical investigation should not interfere with a lactating woman's assessment of the risks and benefits of breastfeeding her infant. The maternal decision to start a clinically indicated medication should be kept separate from any subsequent decision to enroll in a clinical lactation study of that medication.

There are a number of implications of this approach for clinical lactation studies. First, a lactating woman who is breastfeeding should not be approached about participation in a clinical investigation unless such participation is absolutely essential to her personal health and well-being, and there are no reasonable alternative treatments. Under these circumstances, a prudent mother may decide to discontinue breastfeeding given the absence of any information about the effect of that investigational product on a neonate. Second, the investigator has a responsibility for obtaining adequate voluntary and informed consent to the clinical lactation study which must include information about the risks of exposure of her infant to the medication being studied. Although the lactating woman who continues to breastfeed should have been adequately informed by her clinician about the risks of the medication for her breastfeeding infant, it is possible that the information provided by the clinical investigator may be received as new. Thus, the process of informed consent for the clinical lactation study may impact on the woman's prior decision to continue breastfeeding as she again reflects on the risks of the medication to her neonate. If this should happen, the clinical investigator should refer the woman back to her clinician for further discussion of the clinical risks and potential benefits of the medication for herself, and of the risks and benefits of continued breastfeeding for her infant. Third, the risk of
the medication to the exposed infant does not need to be considered a research risk for the purposes of applying 21 CFR 50, Subpart D. The risks that need to be considered are those that are in addition to the drug exposure and would include any involvement of the infant in assessing the scientific objectives of the clinical lactation study. Such procedures may include weighing before and after breastfeeding to determine milk consumption, pharmacokinetic measurements through intermittent blood sampling, biomarker and other pharmacodynamic measurements through intermittent blood sampling and other physiologic parameters, and safety measures for the evaluation of possible adverse effects of the drug exposure through breastfeeding. Both individually and cumulatively, the interventions and procedures contained in the clinical investigation must present no more than a minor increase over minimal risk to the breastfeeding infant given the absence of a prospect of direct benefit (21 CFR 50.53). Given the prior clinical decision for the administration of the medication to the lactating woman for her own health needs, the involved infant can be considered to have a condition which involves the risks of ongoing drug exposure through continued breastfeeding.

**Lactating mother is a healthy volunteer who continues breastfeeding her infant**
When a study drug is administered to a lactating woman as a healthy volunteer, the exposure of the breastfeeding infant to the study drug constitutes a "clinical investigation" even without scientific objectives that require infant involvement. Thus, the exposure of that infant to the study drug must be evaluated under 21 CFR 50, Subpart D. When the study drug offers no prospect of direct benefit to the breastfeeding infant, the regulation requires that the study expose the infant to no more than a minor increase over minimal risk (21 CFR 50.53). In addition, the breastfeeding infant must have a "disorder or condition" for which the clinical investigation results could offer vital information about that condition. Even when a study drug has a sufficient safety profile and administration of that drug to a breastfeeding infant is considered no more than a minor increase over minimal risk (which is extremely unlikely), simply being the infant of a breastfeeding mother is not a disorder or condition under 21 CFR 50.53. Thus, the administration of an investigational product to a healthy lactating woman who intends to keep breastfeeding would expose her infant to a significant and unreasonable risk and is not approvable under 21 CFR 50, Subpart D.

**Lactating mother is a healthy volunteer who stops breastfeeding or pumps and discards her milk during the period of drug exposure**
The question then arises whether a healthy lactating woman who has decided not to breastfeed could be recruited into a clinical lactation study. If a lactating woman is asked to make an enrollment decision at birth, there are scientific and practical obstacles to study participation as the lactating woman would need to mechanically express her milk for a significant period of time before useful milk samples could be obtained. The possibility remains, however, that a breastfeeding woman may make a subsequent independent decision to stop breastfeeding her infant for personal or medical reasons. Under these circumstances, the administration of a study drug to such a lactating woman in a clinical lactation study would be held to the ethical and regulatory standards for the enrollment of a healthy adult volunteer in an FDA regulated clinical investigation under 21 CFR 50 and 56. In other words, if the infant would not receive any breast milk containing the study drug, the additional protections of 21 CFR 50, Subpart D, would not apply. However, the decision to stop breastfeeding should not be affected in any way by the possibility of enrolling in a clinical investigation. Given the health benefits of breastfeeding, an
infant whose mother discontinued breastfeeding for the purposes of enrolling in a clinical investigation would be placed at inappropriate and unjustified risk. It may be difficult to ensure that a woman’s decision to stop breastfeeding her infant is not influenced by her decision to enroll in a clinical investigation. At the very least, a clinical lactation study should not provide any financial or other incentives to encourage participation of breastfeeding women who might otherwise continue breastfeeding their infants.

3. **Identifying and Utilizing Existing Human Data and Deciding When to Conduct a Clinical Lactation Study**

Ideally, FDA would like to have clinical lactation data to inform labeling for all drugs likely to be used by lactating women, and this includes most drugs used in women of reproductive age. Many drugs cross into breast milk to some degree, but the extent of transfer from maternal serum varies widely based on the molecule’s characteristics and the presence or absence of membrane transport proteins. All drug transport proteins in the breast have not been identified. While lipophilic weak bases and compounds that undergo active transport into milk tend to have higher milk/plasma concentration ratios than other substances, all of the following factors influence the amount of drug transfer into breast milk: plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways. After the infant ingests the milk, oral bioavailability of the drug and local gastrointestinal drug effects should also be considered.

The Agency recommends conducting clinical studies in lactating women in the following circumstances:

1) Original or supplemental review of a drug where use is expected by women of childbearing potential. This may include drugs used to treat relatively rare conditions that occur predominantly in women of childbearing age and require chronic drug therapy for disease control, such as multiple sclerosis.

2) Use of a drug by lactating women becomes evident following marketing approval (e.g., via reports in the medical literature or lay press)

3) Marketed medications commonly used by women of childbearing potential including but not limited to: antidepressants, antipsychotics, antihypertensives, anti-infectives, asthma medications, diabetic and pain medications.

Under the following circumstances, clinical lactation studies may not be needed:

1) The drug is not used in lactating women or women of childbearing potential

2) The drug is not systemically available in the mother or orally bioavailable in the infant

3) Well designed lactation studies in humans have already characterized the amount of a drug in breast milk and the total infant daily dose
4) Drugs used to treat medical conditions where breastfeeding is not advised (i.e. HIV).

The International Conference on Harmonisation guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* lists “positive or negative experiences during pregnancy or lactation” as one safety issue that sponsors should explicitly address in the Overall Safety Evaluation section of the Periodic Safety Update Report (PSUR). The sponsor should convey post-marketing information on drug exposures in lactating women to the FDA on a routine basis through PSURs.

Drug manufacturers should use available existing sources of information to help determine if additional data from clinical lactation studies are needed:

1) Published literature, including case reports, on the safety and/or efficacy of the drug in lactating women
2) Published literature on presence or absence of the drug in breast milk of exposed mothers
3) Presence or absence of adverse drug effects in breastfed children of exposed mothers
4) Information from medical specialty groups (e.g., consensus documents or opinion papers).

Interpretation of data from previously completed breast milk studies may be limited by shortcomings in study design. Some studies collected milk samples only during the first few postpartum days before the production of mature milk began. The levels of drug in colostrum may be different than the levels of drug in mature milk. Some studies did not define when milk samples were obtained or whether they included *foremilk* (milk obtained at the onset of feeding by pumping or manual expression) and/or *hindmilk* (milk obtained at the end of feeding by pumping or expression). Human milk fat and protein content change dramatically in the first several weeks postpartum (Hibberd 1982) and over the course of a feeding session. Breast milk is high in lipid and has a pH that is more acidic than plasma. The pH and lipid content of breast milk vary in content by stage of lactation, the time of expression, and diurnally (Neville 2001). Colostrum, produced in the first few days after delivery, has a lower fat content and smaller volume relative to mature milk. Foremilk is more aqueous with a lower fat content relative to hindmilk. These variations in milk character and composition should be accounted for in clinical lactation study design and analyses, because these differences may affect the amount of drug in breast milk and the calculated infant daily drug dose. This said, however, published lactation study data on a particular drug can help inform labeling for nursing mothers and should be submitted to FDA for review.

There is a body of literature from research on environmental exposures and levels of chemicals in breast milk. Some of the techniques used to assess breast milk levels of chemicals and infant exposures may be applicable to the development of clinical lactation studies.

For diagnostic or therapeutic drug products that are administered in single or limited doses and cleared rapidly, clinical management strategies that minimize infant exposure to the therapeutic agent during the short maternal exposure period\(^5\) may be appropriate. However, even in these

\(^5\) The definition of “short maternal exposure period” may vary to some degree with the individual patient and infant. It is a time period during which the mother can reasonably pump and discard her breastmilk (every three to four
situations, a study may be useful to determine levels of drug in breast milk and whether breastfeeding needs to be interrupted at all. Use of diagnostic and therapeutic radiopharmaceuticals that are cleared from the maternal circulation within a few days may be compatible with continued breastfeeding if the mother is motivated to temporarily pump and discard her breast milk.

FDA sometimes requests that pharmaceutical companies establish a pregnancy registry for a drug product likely to be used or with demonstrated use in women of childbearing age. A pregnancy registry is an observational cohort study that prospectively gathers data about the safety and efficacy of drug treatment in pregnant women. For many products, the population of women enrolled in a pregnancy registry may offer an ideal cohort from which to enroll a subset of women in clinical lactation studies and a framework through which to obtain infant outcomes data over a defined period of time.

4. Study Design Considerations

Clinical lactation study objectives and designs will differ based on a drug’s biochemical characteristics and clinical uses (e.g., population, dose, frequency, and route of administration). Based on the amount of drug detected in breast milk and a drug’s oral bioavailability, certain situations may call for studies in mother-infant pairs to determine the extent of systemic infant exposure. It is important that clinical lactation studies are designed and conducted in a manner that:

1) Supports mother/infant breastfeeding pairs
2) Encourages continued (and exclusive) breastfeeding and does not increase the likelihood of breastfeeding failure
3) Exposes only those breastfeeding mothers to drug who have clinical need for treatment
4) Subjects infants to limited blood sampling only when meaningful clinical and public health benefit can result from the knowledge gained.

The following section presents three types of clinical lactation studies. Based on the drug under consideration and whether pharmacokinetic data is needed in lactating women, a milk-only or milk/plasma study design may be used to determine:

- The extent of drug and active drug metabolite transfer into breast milk
- The effects of the drug on milk production
- The effects of the drug on milk composition (fat, protein, immunologic characteristics)
- The estimated drug exposure in the breastfed infant via breast milk.

Data from studies in lactating women coupled with information about a drug in the pediatric population may supplant the need for further lactation studies in the breastfed child. Based on preexisting data and results from mother-only lactation studies, the drug manufacturer can determine whether additional infant-exposure data is needed and whether it can be obtained from mother-infant pair studies.

(hours) while bottlefeeding her infant with previously stored breastmilk or formula and then successfully resume breastfeeding. This time period may be very short or nonexistent for infants who will not feed from a bottle.
It is possible to nest clinical lactation studies within a larger clinical study on safety or efficacy outcomes or in combination with the postpartum assessment of the effects of pregnancy on the PK and/or PD of a drug. For drugs used chronically, the Agency generally recommends that subjects be studied at steady state. However, single dose studies may be sufficient for:

- Drugs that do not accumulate with chronic dosing
- Drugs used to treat acute medical conditions.

Milk and serum samples should be collected in a way that minimally disrupts the mother/baby breastfeeding interaction. Volume and number of samples should be limited to only what is necessary. If infant serum sampling is needed, topical anesthetic should be offered.

**A. Lactating Women, Milk Only Study**

*Lactating women (milk only)* study designs enroll lactating women and include maternal milk sampling throughout the dosing interval or during a specific time period (e.g., a 24-hour period). This study design allows the detection of drug in breast milk and can examine a drug’s effects on milk production and composition. If the amount of drug in breast milk is very low, additional lactation studies may not be needed, depending on the drug and its clinical use and toxicity. Sometimes the resulting data can help identify ways to minimize infant drug exposure, especially for drugs with short half-lives and those used sporadically or intermittently. *Milk only* studies can provide information about optimal timing of maternal dose relative to breastfeeding and identify situations where briefly pumping and discarding milk may be appropriate.

**B. Lactating Women, Milk and Plasma Study**

*Lactating women (plasma and milk)* study designs can provide data on the pharmacokinetics (PK) of a drug in lactating women, the amount of drug transferred into breast milk, and the effects of a drug on milk production and composition. While total infant dose can be estimated, systemic exposure of the infant cannot be measured. Data allow determination of concentration-time profiles and subsequent PK calculations from maternal blood and milk. These designs enrolls lactating women and includes frequent collection of corresponding maternal blood and milk samples. Study subjects may include lactating women who currently use or are planning to use the study medication whether or not they plan to continue breastfeeding their child.

This study design should be chosen instead of a *milk only* design in special situations where maternal pharmacokinetics data is needed to optimize maternal dosing in the postpartum period.

**C. Mother/Infant Pair Design**

*Mother-infant pair* designs can provide information about:

- Drug exposure and PD in the breastfed child
- The PK of the drug in lactating women
- The amount of drug transferred into breast milk
The effects of the drug on milk production and composition.

A mother/infant pair design should never be the first lactation study design performed when the amount of drug transfer into breast milk is unknown. It is appropriate to perform a mother/infant pair design when a milk only study shows significant amounts of drug in breast milk, and the drug is believed to be orally bioavailable. In these situations, it may be important to assess actual drug exposure in the infant. These studies should enroll mother-infant pairs who are currently using or plan to use study medication. There should be collection of corresponding maternal blood and milk samples during a dosing interval or over a specified period of time and limited sampling of infant blood and/or urine. Infant sampling provides information regarding the fraction of drug that is systemically available to the breastfed child. Total clearance of the drug or metabolite by the breastfed child can also be estimated. Data collected in mother-infant pair studies allow for determination of the concentration-time profiles and subsequent PK estimates from maternal blood and/or plasma, breast milk, and infant samples.

If possible, the Agency encourages researchers to incorporate PD endpoints for the breastfed child into the study. PD effects would be directly related to the drug, including extension of the pharmacologic effect or known adverse effects, and be measured objectively (e.g., blood glucose, platelet viscosity).

A mother/infant pair study may be particularly useful for drugs and drug metabolites with the following characteristics:

- High lipophilicity
- Weak bases
- Larger potential for accumulation in breast milk
- High oral bioavailability in the breastfed child
- Wide distribution to multiple organs
- Long half-life

Summation

Using feedback that we receive at the Advisory Committee meeting, we hope to more clearly describe the following:

- Subject inclusion and exclusion criteria and how they might vary with study design
- Situations when longitudinal, multiple arm, and population PK design elements may be useful and appropriate
- Situations where control populations or paired data might be needed
- Milk collection techniques that support ongoing breastfeeding for mother/infant pairs
- When milk/plasma ratios provide additional, clinically useful information beyond that offered by drug concentrations in milk and calculated daily infant dose
- Situations when infant blood sampling is important for defining best clinical practices.

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We hope that this memo provides additional information that will be helpful to you in your deliberations on November 29. Thank you once again for sharing your time, expertise, and perspectives with us. We look forward to working with you.