Guidance for Industry

Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Clinical Pharmacology

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I. INTRODUCTION

This guidance provides recommendations for how and when to conduct clinical lactation studies and how to assess the influence of drugs or biologic products[2] on lactation. The goals of this guidance are to (1) provide the basic framework for designing, conducting, and analyzing clinical lactation studies and (2) stimulate further study and research to assist in rational therapeutics for lactating patients.

Clinical lactation studies can be designed to assess:

- The influence of lactation on maternal pharmacokinetics (PK), and where appropriate pharmacodynamics (PD)
- The extent of drug transfer into breast milk
- The effects of drugs on milk production and composition
- The extent and consequent effects on breast-fed infants[3] of exposure to drugs in breast milk

[1] This guidance has been prepared by the PK in Pregnancy Working Group of the Pregnancy Labeling Task Force, Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Throughout this document, the term *medical product* or *drug* means drug and biological products and their metabolites, including vaccines.

[3] The terms *child(ren)* and *infant(s)* are used interchangeably in this guidance to refer to human breast-feeding offspring of any age.

This guidance will be most helpful when used in conjunction with other pharmacological and clinical literature on the design, conduct, and interpretation of PK studies. Because studies in lactating patients and their breast-fed children require specialized knowledge in a variety of areas, the investigators preparing to design and conduct such studies are encouraged to obtain advice from experts in specific fields (e.g., pediatrics, obstetrics, pharmacology, clinical pharmacology, pharmacometrics, statistics).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Breast milk is widely acknowledged to be the most complete form of nutrition for infants and to include a range of health benefits for breast-feeding women and infants. Accumulated data support the benefits of breast milk for infants including growth, immunity, and development. Specific data show decreased incidence and severity of diarrhea, respiratory infections, and ear infections. Maternal benefits of breast-feeding include reduction in postpartum bleeding, earlier return to prepregnancy 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 targets to increase the percentage of mothers who breast-feed from the current rate to 75 percent in the early postpartum period, 50 percent at 6 months, and 15 percent at 1 year (DHHS Services 2000). The American Academy of Pediatrics (AAP) recommends that all new mothers who are able should breast-feed until the child reaches 1 year of age. A recent survey reports that 69.5 percent of women in the United States initiate breast-feeding and 32.5 percent continue to breast-feed their infants to 6 months of age, reflecting the highest percentage in recent history of women in the United States choosing to breast-feed (Ryan 2002). The AAP considers breast-feeding to be the ideal method of feeding and nurturing infants (AAP Work Group on Breastfeeding 1997).

It is highly likely that a woman will need and take medications while she is breast-feeding, potentially exposing her child to the effects of these medications. Surveys 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 will take medication by 4 months postpartum and 5 percent of nursing mothers receive long-term drug therapy (Bennett 1988).

The presence of a drug in breast milk does not necessarily indicate a health risk for the breast-fed child. Detecting the presence or absence of the drug in milk is only the first step in determining risk. For most drugs, little scientific information is available about the extent of their passage into breast milk, their effects on milk production, their effects on the breast-fed infant, or whether a dose adjustment is needed to treat a lactating woman. Therefore, breast-feeding women and their health care providers must make decisions regarding treatment of maternal

medical conditions in the absence of data. In some cases, this can result in a decision to stop breast-feeding to take needed drug therapy, unnecessarily eliminating the benefits of breast-feeding for mothers and their infants. The AAP has tried to fill the information void regarding infant safety by issuing consensus documents on the use of drugs in lactation or breast-feeding women (AAP 1989, 1994; AAP Committee on Drugs 2001), but data upon which to make these assessments is sparse. Clinical lactation studies would provide much needed additional data on which to base treatment decisions.

Since data on dosing lactating women are rarely available, most clinicians treat lactating women with the dose studied in and recommended for nonpregnant adults. This practice disregards the impact of the physiologic changes that occur during lactation and the effects of additional breast and milk compartments. A variety of potential differences in PK might be important in the postpartum and lactating periods, including differences caused by endogenous hormonal changes, altered body fat proportion, and changes in weight or muscle mass.

Most studies of drugs and breast-feeding focus on health risks for the nursing infant, not the mother. Even when studies collect drug concentrations in maternal serum and breast milk, individual PK is not often characterized, and customary PK parameters (e.g., clearance, half-life) are not reported. Some studies focus on the detection of drug in infant serum compared with maternal serum or milk at a single point in time, but they rarely include comparisons to the non-lactating state or control groups. Most studies do not account for changes in serum protein concentrations and unbound drug in serum, as well as other physiological changes in the early postpartum period, that can affect maternal PK and contribute to variability among data from lactating women (Fleishaker 1989).

Many studies of drugs in breast milk are performed only during the first few postnatal days, or they fail to define when samples were obtained or whether milk samples were drawn from *foremilk*, milk obtained at the onset of feeding or manual expression, or *hindmilk*, milk obtained at the end of feeding or expression. Human milk fat and protein content change dramatically in the first several weeks postpartum (Hibberd 1982). Breast milk is high in lipid and has a pH that is more acidic than plasma and varies in content by stage of lactation, the time of expression, and diurnally (Neville 2001). Colostrum has a lower fat content and smaller volume relative to mature milk. Foremilk is more aqueous with a lower fat content relative to hindmilk. Because of these variations and their potential to alter the effects of drugs during lactation, it is recommended that studies be designed and conducted to capture data that takes these variations into account.

Experts in environmental health have substantial experience in assessing chemical exposures through breast milk. The World Health Organization (WHO) European Centre for Environment and Health has been involved with monitoring environmental exposures via studies on levels of chemicals in human milk, particularly polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) (WHO 1989). A WHO Working Group has also published guidelines for studies on the passage of drugs into breast milk (Bennett 1988, 1996). A 2001 Expert Panel Workshop on Breast Milk Monitoring for Environmental Chemicals in the United States sponsored by the Milton S. Hershey Medical

Center made recommendations on the methods for obtaining human milk, detecting chemicals in those samples, and interpreting and communicating the results of such surveillance and research (Berlin 2002). Some of these methodologies used by the environmental health community are applicable to assessing exposures to pharmaceuticals in breast milk. The environmental health model can also be useful when designing clinical lactation studies.

The consistent application of adequate study designs as described in this guidance would improve the quality and quantity of data available regarding lactation and assist patients and health care providers in making decisions about the use of drugs in lactating women.

III. CONSIDERATIONS FOR WHEN TO CONDUCT A CLINICAL LACTATION STUDY

Circumstances for which the Agency recommends clinical studies in lactating women be done include:

- A drug under review for approval is expected to be used by women of reproductive age
- After approval, use of a drug in lactating women becomes evident (e.g., via reports in the medical literature or lay press)
- A new indication is being sought for an approved drug and there is evidence of use or anticipated use of the drug by lactating women
- Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

If a drug is not used in lactating women or women of reproductive age, then clinical studies in lactation are usually not needed.

Information on experiences and exposure in lactating women will emerge after approval during marketing for virtually all drug products, and sponsors should send information about such experience to the FDA on a routine basis. 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 to be explicitly addressed in the Overall Safety Evaluation section of the Periodic Safety Update Report.

Other sources of information that can help determine whether to conduct clinical lactation studies or which study design to use include (1) publications of safety or efficacy data in lactating women or safety in breast-fed children via exposure to drugs in breast milk, including case reports describing use of a drug in this population, (2) publications on the effects in breast-fed children of maternal ingestion of a drug, and (3) information from medical specialty groups (e.g., consensus documents or opinion papers). Even when use is expected to be rare (e.g., with rare diseases such as multiple sclerosis or infrequent use such as vaccines or radioimaging agents), it is advisable to conduct lactation studies if there is concern that the consequences of uninformed dosages are potentially great.

The applicability and predictability of nonclinical models (e.g., predictions of drug transfer or milk/plasma (M/P) ratios using physicochemical properties of the drug) are still under consideration, but these models do not help in deciding whether to conduct a study in lactating women.

IV. STUDY DESIGN CONSIDERATIONS

The clinical question at hand will determine whether a study of breast milk only, breast milk and maternal PK, or these components plus the infant are warranted. The latter, mother-infant pair studies (1) characterize the PK of the drug in lactating women, (2) measure the amount of parent compound and metabolites transferred into breast milk over the dosing interval, and (3) assess drug exposure in the breast-fed child via breast milk. In addition, depending on the study's primary objective:

- A study of lactating women (plasma and milk) or lactating women (milk only) would be performed before a mother-infant pair study.
- Data from studies in lactating women coupled with what is known about a drug in the pediatric population can supplant the need for further lactation studies in the breast-fed child.
- Any of these strategies could potentially provide data on the extent of drug transfer into breast milk, effect on milk production, and milk composition (e.g., volume, fat, protein, immunologic characteristics).

Regardless of the design chosen, for drugs that are used chronically, the Agency recommends that subjects be studied at steady state. However, for drugs that do not accumulate with chronic dosing, a single-dose study might be sufficient. For drugs that are used to treat acute medical conditions, a single-dose study might be sufficient.

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. Data obtained from single-dose studies are useful and might be considered more acceptable to volunteers and aid in recruitment. Ultimately, standard therapeutic practice (e.g., dose, frequency, and route of administration) is an important consideration in deciding which study design is rational for the drug in question.

A. Mother-Infant Pair Design

The mother-infant pair design allows for data collection in one study to potentially:

- Determine the PK of the drug in lactating women
- Determine the amount of drug transferred into breast milk
- Show effects of drug on milk production and composition
- Assess drug exposure and PD in the breast-fed child

Such a study usually enrolls mother-infant pairs who are planning to or are currently receiving study medication. Its hallmark is the frequent collection of corresponding maternal blood and milk samples as well as sampling of infant blood and/or urine. Infant sampling provides information regarding the fraction of drug that is systemically available to the breast-fed child. Total clearance of the drug or metabolite by the breast-fed child can be estimated as well.

If possible, the Agency encourages PD endpoints for the breast-fed child to be incorporated 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).[4] 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.

This design can be considered if information is already known about the extent of drug transfer into breast milk, but the amount absorbed by the breast-fed child is not known. Other drugs that can be considered for a mother-infant pair design include drugs already approved and known to be used by lactating women who continue to breast-feed and drugs used to treat chronic maternal conditions. Drug or metabolite characteristics that favor selection of this study design include:

- High lipophilicity (weak bases)
- Potential for accumulation in breast milk
- Likelihood of being well absorbed by the breast-fed child
- Wide distribution to multiple organs
- Long half-life

B. Lactating Women Only Designs

1. Lactating Women (Plasma and Milk)

The *lactating women (plasma and milk)* study design provides data on the PK of a drug in lactating women, the amount of drug transferred into breast milk, and effects of a drug on milk production and composition. Infant sampling is not performed in this type of study; therefore, the systemic exposure of the infant cannot be measured (although *total dose* can be estimated). Data allow for determination of the concentration-time profiles and subsequent PK calculations from maternal blood and milk. This design enrolls lactating women and includes frequent collection of corresponding maternal blood and milk samples. Study subjects include lactating women who are planning to receive or are currently receiving study medication, lactating women who need the study medication and will interrupt breast-feeding their infant, and/or healthy lactating volunteers.

[4] Guidance for Industry *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*.

In a sequential or step-wise approach to lactation studies, the *lactating women (plasma and milk)* study design might be considered before the infant is exposed to drug via breast milk in a more complex study. Situations that might favor use of this design include newly approved drugs (especially for drugs with no pediatric data), short-term or acute maternal dosing, and unknown risk of exposure to the breast-fed child. Drug and metabolite characteristics that favor selection of this study design include:

- High lipophilicity (weak bases)
- Presence in milk
- Predictions that drug is present in milk
- Knowledge of a class effect

2. Lactating Women (Milk Only)

The *lactating women (milk only)* study design enrolls lactating women and includes frequent maternal milk samples throughout the dosing interval, a specific time period (e.g., a 24-hour period), or the entire time course of lactating (e.g., months). This study design allows the detection of the presence of a drug in milk. It can also be useful to estimate ways to assess strategies to minimize exposure of the breast-fed child to a drug. Such data can be especially useful for drugs with short half-lives or those associated with sporadic or intermittent use (e.g., migraine therapy). For example:

- *Milk only* studies can provide information regarding timing of maternal dose relative to breast-feeding, the duration recommended to discard milk relative to maternal dose, and when to resume breast-feeding relative to maternal dose or drug exposure.
- A finding that showed the amount of drug in breast milk to be exceedingly low could preclude the need for further studies depending on the drug and its clinical use and toxicity.
- This study design could examine the effect of drug on milk production and composition.

Adequately designed studies would address baseline characteristics and diurnal variation including control group and run-in or lead-in periods prior to drug administration.

C. Other Design Considerations

1. Longitudinal Design

For drugs that are administered chronically or given for several treatment cycles, a longitudinal study design can be considered. Such a study would focus on comparing samples obtained from lactating patients at one postpartum time (e.g., 2-3 months postpartum) to samples obtained from the same patients at a different postpartum time (e.g., 5-6 months) and/or after weaning is complete. Each woman serves as her own control. The post-weaning sampling determines maternal PK and/or PD characteristics from serum sampling only and can capture information at similar times after weaning in all study subjects (e.g., 1 month post-weaning). This longitudinal design would minimize inter-individual variability across the postpartum period. Infant

sampling might also be included in a longitudinal study design (e.g., infant sampling in a longitudinal design might assess infant exposure to drug via breast milk over time in drugs chronically taken by lactating women). Longitudinal infant sampling could assess changes in drug absorption and clearance as well as PD effects at different stages of pediatric development. The Agency encourages that an analytical plan of the study take into consideration the repeat measures characteristics of a longitudinal design.

2. Multiple Arm Design

For drugs that are given acutely (e.g., single dose or short course of therapy), it is generally difficult to perform a longitudinal design using the same patient throughout lactation. One alternative is to conduct a multiple arm study designed to compare different lactating patients at different postpartum times (e.g., a sample of women each at 2-3 months and 5-6 months postpartum). Each woman serves as her own control and has PK and/or PD determinations performed after weaning is complete.

In certain circumstances drug therapy is no longer clinically indicated later in the postpartum period or when weaning is complete. If possible a single-dose PK/PD study can be performed to allow each woman to serve as her own control. This applies to drugs that possess linear PK. If it is impossible to administer drug in the same women (study population), then an additional arm of the study using a different population of postpartum women (appropriately matched healthy female volunteers, as a last resort) would be included.

3. Study Participants

Optimally, study participants represent a typical patient population, including race and ethnicity, for the drug to be studied. Maternal factors with significant potential to affect lactation (e.g., weight, gravity, parity, stage of lactation, postpartum status, and episodes and duration of previous lactation) and the PK of a drug to be studied (e.g., diet, smoking, alcohol intake, concomitant medications, ethnicity, other medical conditions) are important considerations. Infant factors (e.g., age, term versus preterm neonates, extent of breast-feeding, and age-related changes in absorption, distribution, metabolism, and excretion) also might warrant special consideration, depending on the drug. It is important to apply uniform diagnostic factors to all patients enrolled in the study to ensure uniformity of diagnosis of the condition for which treatment is being given and to reduce disease-specific variability in PK.

For drugs that are hepatically metabolized and known to exhibit genetic polymorphism (e.g., CYP2D6 or CYP2C19), the metabolic status of the enrolled subjects (maternal and infant) can be important factors when analyzing the results of the study.

4. Controls

Ideally the lactating woman would serve as her own control, for example, by undergoing PK assessment(s) during lactation and again after weaning is complete. For PK/PD studies, potential control groups include healthy non-lactating female volunteers or non-lactating female

volunteers with the medical condition of interest. Studies that evaluate the effect of drug on milk production and composition could include lactating female volunteers who are not using the test drug or, preferably, lactating female volunteers who have the medical condition of interest. If female volunteers are used as controls, the Agency recommends matching them to study subjects (e.g., postpartum status, age) and identifying time windows (e.g., 3-4 months postpartum) to account for variability in physiologic postpartum changes. The Agency recommends that the study protocol provide the rationale for the make-up of the control group selected.

5. Sample Size

Determination of an adequate sample size depends on the objective and design of a study. For a study that examines plasma PK in the mother or lactating woman, the Agency recommends that the number of patients enrolled in the study be sufficient to detect clinically significant differences (e.g., PK differences large enough to warrant dosage adjustments). The PK variability of the drug as well as the PK and PD relationships for both therapeutic and adverse responses (therapeutic range) would inform this decision. Sample size considerations include PK and PD variability for the drug being studied, the study design (i.e., single-dose vs. multiple-dose), and the variability in lactation physiology. Inter- and intra-subject variability for mother and breast-fed child can be considered depending on the design and primary objective of the study. For a population PK approach, sparse sampling with a larger number of subjects might be considered if patients sufficiently span the postpartum time periods of interest.[5]

The final number of patients enrolled would likely be in excess of the number originally calculated by standard sample size calculations to take into account dropouts and subsequent exclusion from the study, especially for longitudinal study designs. The institution conducting the study can rely on past experience to aid in understanding the usual number of patients who complete a clinical lactation study, given dropouts or other issues.

Since *milk only* studies are more exploratory in nature, a minimum of 6-8 subjects can be sufficient.

6. Sample Collection and Analysis

The Agency recommends that the frequency and duration of sampling be sufficient to accurately detect the outcome selected (e.g., estimate the relevant PK parameters for the parent drug and metabolites — see Section V., Data Analysis). It is important to collect samples to characterize the complete dosing interval; each breast would be completely emptied and the volume of milk recorded. An electric milk pump is recommended since milk composition can vary with the method used. Separate collection containers would be used for each milk collection. Separate milk samples obtained within each collection interval might be pooled (e.g., 4-8 hour post-dosing) and an aliqout removed for analysis. Multiple collection time intervals of milk would permit the full milk concentration-time profile and subsequent estimation of PK parameters in

[5] Guidance for Industry *Population Pharmacokinetics*.

milk. It is recommended that the protocol specify instructions for sample handling, especially for milk samples (e.g., methods to minimize contamination).

The Agency recommends that milk be completely expressed from each breast, mixed, and a sample removed for analysis. For *mother-infant pair* studies, the infant can be bottle-fed expressed milk. Infant milk consumption can be determined by measuring the volume of expressed breast milk consumed or, alternatively, by weighing the infant before and after feeding. Weighing the infant before and after feeding can be a more accurate method of determining milk consumption because it accounts for any milk volume lost via dribbling, drooling, and burping the breast-fed infant. This post-feeding weight accounts for any infant voiding (e.g., urine, stool) that occurred during feeding. For characterization of the terminal elimination phase of the drug in the breast-fed child, previously collected drug-free breast milk or formula can be substituted at subsequent feedings.

The Agency recommends that total and unbound concentrations of drug and metabolites in plasma be determined; for other biological matrices (e.g., breast milk) total concentrations of drug and metabolites are likely sufficient. It is important that method validation address accuracy, precision, selectivity, sensitivity, reproducibility, and stability.[6] Because of varying lipophilicity among drugs, it is also important to assay milk samples for milk fat.

Alternative, noninvasive pediatric sampling strategies (e.g., saliva, tears) might also be used to estimate drug levels in infants. However, drug concentrations obtained from alternative fluids (e.g., saliva, tears) might not be equivalent to those obtained from plasma. Sponsors are, therefore, encouraged to demonstrate the relationship of the drug concentration between plasma and alternative fluids in adults. Estimating infant drug exposure via breast milk solely from excretion of unchanged drug in infant urine can be of limited utility because of the difficulty with urine collection and the variability of renal clearance and urine production in infants.

7. Population PK Studies

A population PK approach is a possible alternative way to enroll lactating women (and breast-fed children) in PK studies and minimize the number of blood draws and PD assessments. The population PK approach assesses the impact of various covariates on the PK of a drug. Practical difficulties in conducting a population study can limit the value of such a study. Validated sparse sampling methods based on optimal sampling theory and limited sampling methods are useful in determining the optimal sampling times to best estimate PK parameters. Further information on this approach is available in Agency guidance.[7]

8. Pharmacodynamic Assessments

Whenever appropriate, the Agency encourages PD assessment to be included in clinical lactation studies and discussed with the appropriate FDA review staff. Given the assumption of an

[6] Guidance for Industry *Bioanalytical Method Validation*.
[7] Guidance for Industry *Population Pharmacokinetics*.

unaltered PK/PD relationship, PK measurements alone would generally be recommended for lactation studies, although PD studies might sometimes provide additional useful information. If studied, the PD endpoints chosen can be based on the pharmacological characteristics of the parent drug and metabolites (e.g., extent of protein binding, therapeutic range, and the behavior of other drugs in the same class in lactating patients). Similarly, biomarkers might be used to measure PD endpoints of interest. PD assessments in the breast-fed child can also be considered (e.g., heart rate and rhythm response to maternal administration of drug).

V. DATA ANALYSIS

The primary intent of the data analysis is to estimate or assess the clinical impact of drug use by lactating women. The categorization of stage of lactation (or weeks postpartum) might direct the type of analysis performed. Special analytical considerations are important for longitudinal study designs and the baseline comparisons; however, data analysis typically consists of the following steps:

- Estimation of PK parameters in maternal serum/plasma, breast milk, and the breast-fed child
- Comparison of PK parameters in the lactating women to those in non-lactating women
- Estimation or measures of exposure of the drug in the breast-fed child
- Estimation of alterations of breast milk (e.g., production and composition) and the resulting impact on the breast-fed child
- Development of dosing recommendations including an assessment of whether dosage adjustment is warranted in lactating patients
- Estimation of ways to minimize exposure of the breast-fed child to drug via breast milk (e.g., timing of maternal dose relative to breast-feeding, recommended duration to discard milk relative to maternal dose, resumption of breast-feeding relative to maternal dose or drug exposure)

A. Parameter Estimation

The Agency recommends that total and unbound plasma and milk concentration data (and urinary excretion data, if collected) be used to estimate PK parameters of the parent drug and metabolites. Maternal plasma PK parameter estimates might include: the area under the plasma concentration curve (AUCp; AUC_{0-t} or $AUC_{0-\infty}$ in single-dose studies and $AUC_{0-\tau}$ at steady state), peak plasma concentration (C_{max}), time to peak plasma concentration (t_{max}), plasma clearance (CL_T) or apparent oral clearance (CL/F), apparent volume of distribution (V_Z/F or V_{ss}/F), and terminal half-life ($t_{1/2}$). The Agency recommends that the area under the milk concentration-time curve over 24 hours (AUCm; AUC_{0-24}) be calculated. PK parameters would be expressed in terms of total and unbound concentrations. For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80 percent), description and analysis of the PK in terms of total concentrations is recommended. Infant PK parameter estimates can be obtained, as appropriate. The PK parameters of metabolites in maternal plasma, in breast milk, and ingested by the breast-fed child can be estimated. If the samples (e.g.,

number, volume) obtained from the breast-fed child do not permit determination of total and unbound concentrations, the average fraction of drug bound would then be determined. Noncompartmental and/or compartmental modeling approaches to parameter estimation are recommended.

The amount of drug or metabolite consumed in a day by the breast-fed infant, the infant dosage, can be determined:

> Daily Infant Dosage (mg/day) = total drug excreted in milk and consumed by the infant per day.

Theoretically, any time frame could be chosen (e.g., dosing interval); however, it is likely easier to interpret daily dosage information.

The Agency recommends that the infant dosage be calculated by summing the product of drug concentration times the volume of milk for each sample time:

> Daily Infant Dosage (mg/day) = Σ (total drug concentration in each milk collection × expressed milk volume in each milk collection)

EXAMPLE: Daily infant dosage
The data in the table below reflect milk collected for 24 hours with the following drug concentrations and volumes for each sampling interval.

Sample Collection Interval (hrs)	Milk Drug Concentration (µg/mL)	Milk Volume Expressed (mL)	Drug in Milk (µg)
0-4	0.27	98	26.46
4-8	0.24	146	35.04
8-12	0.16	125	20.0
12-16	0.022	110	2.42
16-24	0.008	245	1.96

In the example above, the Daily Infant Dosage is equal to 85.88µg or 0.086 mg/day

Alternatively, the infant daily dose might be estimated with the following equation:

> Estimated Daily Infant Dosage (mg/kg/day) = M/P × average maternal serum concentration × 150 mL/kg/day

In this case M/P (milk-to-plasma ratio) is the ratio of AUC_{milk} to AUC_{plasma}. The average maternal serum concentration refers to $AUC_{0-\infty}$/dosing interval after maternal ingestion of a single dose of drug or $AUC_{0-\tau}$/dosing interval at steady state during chronic maternal dosing (Bennett 1988, 1996). When using this approach to estimate daily infant dosage, the AUC is either the AUC from time zero to infinity ($AUC_{0-\infty}$) after maternal ingestion of a single dose of

drug or the AUC within a dosing interval ($AUC_{0-\tau}$) at steady state during chronic maternal dosing.

Calculation of the M/P ratio from single paired maternal milk and plasma concentrations obtained at one sampling time is not recommended. The M/P ratio using AUCs has been shown to provide a more accurate estimate of breast milk content of drug compared to the milk to plasma ratio from isolated samples (Begg 1999; Wojhar-Horton 1996; Wilson 1985). The standardized milk consumption of 150 mL/kg/day, the mean milk intake of a fully breast-fed 2-month old infant (Begg 1999; Bennett 1988; Hagg 2000; Kristensen 1999) is used.

The Agency recommends that the percent of the weight-adjusted maternal dose consumed in breast milk over 24 hours be calculated:

$$\% \text{ Maternal Dosage} = (\text{Infant Dosage (mg/kg/day)}/\text{Maternal dosage (mg/kg/day)}) \times 100$$

Similarly, this might be calculated for a dosing interval. If the pediatric or infant dose is known (i.e., the drug is approved for pediatric use), it is possible to estimate the percent weight-adjusted pediatric dose ingested as well.

The infant serum concentration is probably the most direct measure of infant risk from a drug received from breast milk. If infant serum data are not collected, it is possible to estimate the average infant serum concentration (Css,ave) by:

$$Css,ave = F \times \text{infant dosage}/CL$$

where F is the bioavailability and CL is the drug clearance in the infant, if these data are known for the pediatric population.

If other methods are used to determine infant exposure to drug from breast milk, those methodologies should be comparable to those in this guidance.

B. Development of Dosing Recommendations for Lactating Women

If, based on studies, a dosage adjustment is important when a woman is lactating, the Agency recommends that the labeling describe the relationship between the drug's PK and lactation. Typically, the dose is adjusted to produce a comparable range of unbound plasma concentrations of drug or metabolites in both normal adult patients and lactating patients. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal. For some drugs, lactation may not alter PK sufficiently to warrant dosage adjustment. A sponsor might make this claim by providing an analysis of the study data to show that the PK measurements most relevant to therapeutic outcome in lactating patients are similar or equivalent to those in normal adult or post-weaning patients.

Results of the impact of lactation on the maternal PK of medical products can be reported as 90 percent confidence intervals about the geometric mean ratio of the observed PK measures.

When an impact of lactation is clearly present (e.g., a comparison indicates twofold or greater change in systemic exposure measures), the sponsor would provide specific recommendations regarding the clinical significance of the interaction based on what is known about the dose-response and/or PK/PD relationship. This information would form the basis for reporting study results and for making recommendations in the package insert.

The sponsor may wish to make specific claims in the package insert that no impact is expected from lactation on the PK of a medical product. In this instance it is possible for the sponsor to recommend specific *no effect* boundaries or clinical equivalence intervals for the impact of lactation on the PK of a medical product. There are two approaches to define *no effect* boundaries.

Approach 1: The sponsor would recommend, prior to the conduct of the studies, specific *no effect* boundaries for the mean geometric ratio of C_{max} and AUC. They might be based on population (group) average dose and/or concentration-response relationships, PK/PD models, and other available information. If the 90 percent confidence interval for the systemic exposure measurement in the lactation study falls completely within the *no effect* boundaries, the sponsor can conclude that no clinically significant impact of lactation on the PK of the medical product was present.

Approach 2: In the absence of *no effect* boundaries defined above, a sponsor might use a default *no effect* boundary of 80-125 percent. When the 90 percent confidence intervals for systemic exposure ratios fall entirely within the equivalence range of 80-125 percent, standard Agency practice is to conclude that no clinically significant differences are present.

If, based on lactation studies, there is a need for dose adjustment while a women is lactating, the labeling would describe the relationship between the medical product's PK and lactation. Typically the dose regimen is adjusted to produce comparable C_{max} and AUC values. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal.

C. Development of Recommendations to Minimize Infant Drug Exposure from Breast Milk

It is possible to use data from kinetic profiles in milk to provide recommendations for ways to minimize exposure of the breast-fed child to a drug via breast milk. The Agency recommends that the labeling describe the relationship between maternal drug administration and breast-feeding, taking into account drug kinetics such as half-life in milk. For example, ways to minimize exposure to drug in breast milk might include information regarding (1) the timing of maternal dose relative to breast-feeding, (2) the duration of time relative to maternal drug administration to discard breast milk (e.g., "pump and dump"), and (3) how long to wait until resuming breast-feeding relative to maternal dose.

VI. LABELING

The Agency recommends that labeling reflect the data from clinical lactation studies and, if known, dosing recommendations during lactation. The labeling would reflect the data pertaining to the effect of lactation on the PK and PD (if known) obtained from studies conducted. If the PK and/or PD are altered during lactation, the Agency recommends that the appropriate description of such and recommendations for dosing be stated in labeling. The labeling would contain information pertaining to drug transfer into breast milk, the exposure of breast-fed infants to drugs in breast milk, and the drug effect on milk production and composition, if known. Non-positive findings are to be interpreted as indicating failure to detect an impact of lactation on PK or PD rather than lack of an effect.

The various permutations of intrinsic drug characteristics and the effect of lactation on drug performance preclude precise specification of how such drugs can be labeled. The following comments offer general suggestions on labeling.

A. Clinical Pharmacology

1. Pharmacokinetics Subsection

This section would include information pertinent to lactation on the:

- Disposition of parent drug and metabolites, if applicable
- Effects of lactation on protein binding, if applicable

2. Special Populations Subsection

This section would recapitulate, in brief, the PK changes found in lactation and, if needed, dosing adjustments for lactating patients. The section would briefly describe any data regarding drug transfer into breast milk, the exposure of breast-fed infants to drugs in breast milk, and the drug effect on milk production and composition, if known. This information would be based on the studies performed as described in this guidance. Reference would be made to the PRECAUTIONS/NURSING MOTHERS and the DOSAGE AND ADMINISTRATION sections. The following text provides examples of possible wording for these sections.

The simplest situation involves drugs for which lactation has little to no effect on PK:

> *The disposition of [Drug X] was studied in [number of] lactating women from [a through b months postpartum]. Lactation has little to no influence on [Drug X] pharmacokinetics and no dosing adjustment is needed.*

Similarly, for drugs whose PK is influenced by lactation, the following statement can be modified in accordance with what is known about the drug (e.g., active or toxic metabolite) and from the studies performed in accordance with this guidance:

The disposition of [Drug X] was studied in [number of] lactating women from [a through b months postpartum]. Elimination of the drug (and metabolite, if applicable) is significantly changed during lactation. Total body clearance of (unbound, if applicable) [Drug X]/metabolite was [reduced/increased] in lactating women compared to non-lactating women. The terminal half-life of [Drug X]/metabolite is [prolonged/decreased] by [Y-fold]. (See DOSAGE AND ADMINISTRATION.)

Similarly, the following statement can be modified as appropriate to describe drug transfer into breast milk:

A [dose (mg), single or multiple dose] of [Drug X] was administered [route of drug administration (e.g., oral, intravenous)] to [number of] lactating women who were [a through b months postpartum]. Breast milk obtained for [c hours] after dosing revealed a maximum concentration of [y concentration] [t_1 time] after dosing and drug concentrations in milk rapidly declined over [the next time duration, t_2 time]. The estimated daily infant dose for [Drug X] from breast milk is [z dose or z mg] which represents [_____%] of maternal dose and [_____%] of the lowest approved pediatric dose (if applicable). No drug was detectable in milk samples obtained [t_3 time] or later after dosing.

B. Precautions/Nursing Mothers

In addition to standard labeling for use in lactation, if studies performed during lactation demonstrate clinically important changes, the Agency recommends that such information be included in the PRECAUTIONS/NURSING MOTHERS section with cross-reference to DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections. It is recommended that labeling contain information, to the extent possible, based on the lactation study conducted, including:

- PK/PD in lactation
- The effect of drug on milk production (e.g., quality and quantity of milk including milk production and composition)
- The presence of drug or metabolite in milk, including the limitation of the assay used if drug/metabolites are not detected in milk
- The amount of drug or metabolite in breast milk over a 24-hour period
- The amount of drug or metabolite consumed daily by the breast-fed infant
- The percent of maternal dose delivered via breast milk and consumed daily by the breast-fed infant (i.e., daily dose in human milk compared to the usual adult dose, or pediatric dose, if known)
- Possible ways to minimize exposure in the breast-fed child to drug via breast milk taking into account drug kinetics such as half-life in milk (e.g., timing of maternal dose relative to breast-feeding, the duration to discard breast milk relative to maternal dose, and how long to wait until resuming breast-feeding relative to maternal dose)
- Effects of drug exposure via breast milk in the breast-fed infant
- PK of drug in the breast-fed infant

C. Dosage and Administration

As appropriate, the following information would be included:

- A statement describing the relationship between [Drug X]'s clearance and lactation
- A statement describing how the dose would be adjusted during lactation within the approved therapeutic range:

  The dose of [Drug X] should be [increased/decreased] by [_____%] during lactation.

- If no dose adjustment is needed, the following statement might be used:

  The influence of lactation on [Drug X] pharmacokinetics is sufficiently small that no dosing adjustment is needed.

- A statement cross-referencing the Precautions/Nursing Mothers section of labeling when possible ways to minimize exposure in the breast-fed child with respect to timing of maternal dose relative to breast-feeding are included in the Precautions/Nursing Mothers section.

VII. CONSIDERATIONS FOR FUTURE RESEARCH

Although nonclinical models (e.g., mechanistic, in vitro, animal, physicochemical-based, and physiological-based PK (PBPK)) have demonstrated limited success in predicting the amount of drug in breast milk and in predicting infant exposures to drug in breast milk (Oo, *Transport of Cimetidine*, 1995; Oo, *Alprazolam Transfer*, 1995) the applicability of nonclinical predictive models is still under investigation. Because of this, data obtained from clinical lactation studies would enable testing of the predictive value of these nonclinical models. The incorporation of the additional information obtained from clinical lactation studies into nonclinical models would strengthen the association between predicted and observed exposures and optimally improve the predictability of such approaches.

BIBLIOGRAPHY

American Academy of Pediatrics (AAP), 1989, American Academy of Pediatrics Committee on Drugs: Transfer of Drugs and Other Chemicals into Human Milk, Pediatrics, 84(5):924-36.

American Academy of Pediatrics (AAP), 1994, American Academy of Pediatrics Committee on Drugs: Transfer of Drugs and Other Chemicals into Human milk, Pediatrics, 93(1):137-50.

AAP Committee on Drugs, 2001, Transfer of Drugs and Other Chemicals into Human Milk, Pediatrics, 108(3):776-89.

AAP Work Group on Breastfeeding, 1997, Breastfeeding and the Use of Human Milk, Pediatrics, 100(6):1035-1039.

Begg, EJ, SB Duffull, DA Saunders et al., 1999, Paroxetine in Human Milk, Br J Clin Pharmacol, 48:142-147.

Bennett, PN (ed), 1988, Drugs and Human Lactation, Amsterdam: Elsevier.

Bennett, PN (ed), 1996, Drugs and Human Lactation, 2nd edition, Amsterdam: Elsevier.

Berlin, CM Jr, JS LaKind, BR Sonawane et al., 2002, Conclusions, Research Needs and Recommendations of the Expert Panel: Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States, J. Toxicol. Environ. Health, Part A, 65:1929-1935.

Fleishaker, JC, N Desai, and PJ McNamara, 1989, Possible Effect of Lactational Period on the Milk-to-Plasma Drug Concentration Ratio in Lactating Women: Results of an In Vitro Evaluation, J Pharm Sci, 78(2):137-141.

Hagg, S and O Spigset, 2000, Anticonvulsant Use During Lactation, Drug Saf, 22:425-440.

Hibberd, CM, OG Brooke, ND Carter et al., 1982, Variation in the Composition of Breast Milk During the First 5 Weeks of Lactation: Implications for the Feeding of Preterm Infants, Arch Dis Child, 57(9):658-662.

Kristensen, JH, KF Ilett, LP Hackett et al., 1999, Distribution and Excretion of Fluoxetine and Norfluoxetine in Human Milk, Br J Clin Pharmacol, 48:521-527.

Neville, MC, 2001, Anatomy and Physiology of Lactation, Pediatr Clin North Am, 48(1):13-34.

Oo, YC, RJ Kuhn, N Desai, and PJ McNamara, 1995, Active Transport of Cimetidine into Human Milk, Clin Pharmacol Ther, 58:548-555.

Oo, YC, RJ Kuhn, N Desai et al., 1995, Pharmacokinetics in Lactating Women: Prediction of Alprazolam Transfer into Milk, Br J Clin Pharmacol, 40:231-236.

Ryan, AS, Z Wenjun, and A Acosta, 2002, Breastfeeding Continues to Increase into the New Millennium, Pediatrics, 110:1103-1109.

U.S. Department of Health and Human Services (DHHS), 2000, Healthy People 2010: Understanding and Improving Health, 2nd ed., Washington, DC: U.S. Government Printing Office (http://www.health.gov/healthypeople/document/).

World Health Organization, 1989, Levels of PCBs, PCDDs and PCDFs in Breast Milk: Results of WHO-Coordinated Interlaboratory Quality Control Studies and Analytical Field Studies, in Yrjanheikki EJ (ed), Environmental Health Series RPt 34, Copenhagen: World Health Organization Regional Office for Europe.

Wilson, JT, RD Brown, JL Hinson, and JW Daily, 1985, Pharmacokinetic Pitfalls in the Estimation of the Breast Milk/Plasma Ratio for Drugs, Ann Rev Pharmacol Toxicol, 25:667-689.

Wojnar-Horton, RE, LP Hackett, P Yapp et al., 1996, Distribution and Excretion of Sumatriptan in Human Milk, Br J Clin Pharmacol, 41:217-221.