Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

DRAFT GUIDANCE

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

May 2019
Clinical/Medical

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for sponsors conducting clinical lactation studies. The Food and Drug Administration (FDA or Agency) has required lactation studies under section 505(o)(3) of the Food, Drug, and Cosmetic Act (FD&C Act) under some circumstances and is considering additional circumstances in which lactation studies may be required. In addition, sponsors in some circumstances may elect to conduct lactation studies absent a requirement or request from the Agency.

This guidance reflects FDA's current recommendations regarding pre- or post-marketing lactation studies by drug sponsors.[2] This guidance provides information to facilitate the conduct of lactation studies. Such studies can inform breastfeeding with drug use recommendations included in the *Lactation* subsection of labeling.

The recommendations in this guidance reflect discussions from the 2007 Pediatric Advisory Committee meeting[3] and the 2016 Lactation Workshop,[4] which considered how data from clinical lactation studies can inform the safety of a drug when used during lactation.[5] This draft guidance replaces the draft guidance for industry *Clinical Lactation Studies — Study Design, Data Analysis, and Recommendations for Labeling*, which published in February 2005.

[1] This guidance has been prepared by the Division of Pediatrics and Maternal Health in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] See https://wayback.archive-it.org/7993/20170403222238/https://www.fda.gov/ohrms/dockets/ac/oc07.htm#pac.

[4] See https://www.fda.gov/Drugs/NewsEvents/ucm486761.htm.

[5] Wang J, Johnson T, Sahin L, et al., 2017, Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary, Clinical Pharmacol Ther, 101(6):736–744.

This guidance does not address specific lactation labeling recommendations. These topics are addressed in 21 CFR 201.57(c)(9)(ii) and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014).[6]

In general, FDA's guidance documents 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

Despite significant efforts to improve the quantity and quality of information in labeling for drug use during lactation, there remains a paucity of human data. Therefore, lactating women and their health care providers often must make decisions about drug treatment and continuation of breastfeeding during therapy without quality human data in labeling. For that decision to be evidence based, lactating women and health care providers would need information including, at a minimum, the amount of drug in human milk, the effect of the drug on milk production, and an understanding of the risks posed by the drug on the breastfed infant based on expected levels of exposure and adverse drug event data.

Data from clinical lactation studies, along with other relevant data (e.g., drug physicochemical characteristics, mechanism of drug entry into breast milk, data from nonclinical studies, important infant factors) can be analyzed to evaluate the safety of a drug when used during lactation. The data can also be used to develop recommendations to minimize infant exposure, when appropriate.

III. CONSIDERATIONS FOR CLINICAL LACTATION STUDIES

A. Considerations for Conduct of a Clinical Lactation Study

FDA has required lactation studies under section 505(o)(3) of FD&C Act under some circumstances and is considering additional circumstances in which lactation studies may be required. In addition, sponsors in some circumstances may elect to conduct lactation studies absent a requirement or request from the Agency.

FDA encourages sponsors to consider conducting a clinical lactation study whenever such study would be appropriate, even if the study is not being required by the Agency. The following are situations when a sponsor may wish to consider whether conducting a clinical lactation study would be appropriate:

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- 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)

These and other factors should be considered on a case-by-case basis.

B. Ethical Considerations

FDA-regulated clinical trials, including lactation studies, must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR part 56, Institutional Review Boards, and 21 CFR part 50, Protection of Human Subjects (including subpart D, Additional Safeguards for Children in Clinical Investigations)). Sponsors should consider the following ethical considerations with respect to three populations of lactating women who may potentially participate in clinical lactation studies:[7]

1. Lactating women who are prescribed the drug, which is the subject of the lactation study, as part of standard clinical care

    - If a lactating woman was prescribed and is continuing to take a medically necessary drug, it is not necessary to stop the drug for the purposes of enrollment in a research setting. It would be ethically acceptable to enroll women who have already made a decision to take a medically necessary drug while breastfeeding and allow them to continue breastfeeding while taking the drug. The drug exposure, specifically, to the infant would be considered a clinical risk. Any risks associated with the research would still need to be described.

2. Women in a research setting who are administered an investigational drug

    - In a research setting, where a woman who is currently breastfeeding starts an investigational drug for a disorder or condition, breastfeeding must be discontinued for the duration of the study because the risks of the exposure to the drug in the breastfeeding infant may outweigh the benefits. The potential drug exposure of a breastfeeding infant must be considered a research risk (and offers no clinical benefit to the infant).

7 Wang J, Johnson T, Sahin L, et al., 2017, Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary, Clin Pharmacol Ther, 101(6):736–744.

- It is acceptable to enroll breastfeeding women who are participating in a clinical trial of an investigational drug in clinical lactation studies if the breastfeeding woman agrees to temporarily pump and discard milk to avoid exposing an infant to the investigational drug. The length of time that the milk will need to be discarded should be specified in the protocol and will vary depending on factors such as the half-life of the drug.

3. Women who are healthy volunteers and are administered the investigational drug for the purpose of clinical research

- In a research setting where a healthy woman who is currently breastfeeding volunteers for a clinical lactation study, breastfeeding must be discontinued for the duration of the study so that an infant is not exposed to the investigational drug.

C. Study Design Considerations

In considering the appropriate type of clinical lactation study to conduct, the sponsor should consider strategies that minimize the burden of data collection on the mother while obtaining adequate data. The study should avoid disruption of the breastfeeding routine and support return to breastfeeding if breastfeeding must be temporarily discontinued. Additionally, use of remote clinical study sites may provide access to a patient population that may not otherwise be willing or able to participate. Home health care nursing visits can be particularly important to successful recruitment and conduct of lactation studies of drugs with longer half-lives, when many visits occur over a period of several weeks.

1. General Study Designs

Sponsors should consider the following types of study designs for clinical lactation studies:

- Lactating woman (milk-only) study

  - A milk-only study can be used to detect the presence of a drug in breast milk, quantify or estimate the total amount of a drug transferred into breast milk (when plasma concentrations are known), and evaluate the effects of a drug on milk production (when milk production in lactating women not taking the drug is known). If the concentration of a drug in breast milk is found to be clinically relevant, this finding could lead to further studies.

  - In general, FDA recommends milk-only studies unless there is a reason to conduct another type of clinical lactation study.

- Lactating woman (milk and plasma) study

  - Milk and plasma collection in lactating women can provide pharmacokinetic (PK) data on a drug in a lactating woman, the amount of drug transferred into breast milk, and the effects of a drug on milk production. In certain situations, the PK data of the

drug may be unknown in lactating women such that obtaining such data would provide additional information in the amount of drug transferred into breast milk (e.g., when there is a concern for accumulation of a drug in breast milk).

- Mother-infant pair study

  – Mother-infant pair studies that include assessment of drug concentrations in infants can provide information on absorption of drugs in infants through breast milk and safety assessments in infants enrolled in these studies. A sponsor should consider this design if information is already available about the extent of drug transfer into breast milk including evidence that the drug accumulates in breast milk and if the drug is likely to be absorbed by the breastfed infant.

2. Other Study Design Considerations

In addition to the type of study design, sponsors should also consider the following study design issues:

- Single-dose design

  – For drugs that are given acutely (e.g., single-dose drug, drugs that do not accumulate with chronic dosing), a single-dose study may be sufficient.

- Longitudinal design

  – For drugs that are administered chronically or given for several treatment cycles, a sponsor may consider a longitudinal study design. Under such a design, samples are obtained from each lactating woman at different time points (e.g., at 2–3 months and then again at 5–6 months).

- Multiple-arm design

  – For drugs that are given acutely (e.g., single dose or short course of therapy), a multiple-arm study can be used to compare different lactating patients at different postpartum times. Under such a study, samples are obtained from different lactating women at different time points (e.g., at 2–3 months, 5–6 months).

3. Study Subject Considerations

The following maternal and infant factors can affect the results of a clinical lactation study. These factors should be collected in all lactation studies.

- Maternal factors

- Maternal weight, age, gestational age at delivery, stage of lactation, length of time postpartum, smoking, alcohol intake, concomitant drugs, ethnicity, race, and existing medical conditions should be collected and reported for each study subject.

- The study should specify subjects who exclusively breastfeed versus those who supplement with infant formula. Although FDA recommends that studies include only women who exclusively breastfeed, including women who are supplementing with infant formula provides *real life* data and may allow for easy collection of pumped milk that would otherwise be discarded. However, studies should report the extent of use of infant formula.

- Infant factors (for infants enrolled in mother-infant pair studies)

  - Age, weight, history of prematurity, drugs, existing medical conditions, ethnicity, and race should be collected and reported for each infant enrolled in a mother-infant pair study.

4. Sample Size Considerations

Sponsors should consider the following for sample sizes in clinical lactation studies:

- Sample size considerations include PK variability for the drug being studied, the study design (i.e., single dose versus multiple dose), and the variability in lactation physiology.

- A sponsor should consider the inter- and intra-subject variability for both mother and breastfed infant, depending on the design and primary objective of the study. For example, an increase to the sample size may be warranted if there is evidence of high inter- or intra-subject variability.

D. Milk Sampling Methods

For milk sampling during clinical lactation studies, sponsors should consider the following:

- Type of milk collected

  - The study design should specify the type of milk to be collected. For example, differences in composition of foremilk versus hindmilk should be accounted for with some drugs because transfer of drugs may be affected by the composition of the milk (e.g., foremilk contains more water and less fat which may affect the transfer of lipophilic drugs).

  - Sampling should ideally take place after the development of mature milk (after approximately 10 days postpartum). Colostrum or transitional milk collection may not reflect drug transfer in mature milk because drug transfer may be transiently increased because of a more porous mammary epithelium. However, sampling of colostrum or transitional milk may be important under certain circumstances. For

example, if concern exists about exposure of the drug in the immediate neonatal period, colostrum samples may be needed.

- The specific timing of the milk sample relative to both the dose and days postpartum should routinely be collected.

- Milk sampling method

  - In general, FDA recommends the collection of the entire milk volume from both breasts over 24 hours. Sampling should occur when drug exposure is at steady state during chronic maternal dosing. For drugs with dosing intervals of more than 24 hours, consideration should be made to collect milk over the entire dosing interval or to collect 24-hour samples during the expected time to peak plasma concentration. The sampling schedule should take into consideration a drug's known PK parameters and be adjusted for drugs with longer dosing intervals, balancing the need for adequate data collection with feasibility.

  - After the milk is collected, the necessary aliquots for assay should be saved using proper storage methods. The remainder of the milk collected can be refed to the infant under certain circumstances (see section III. B., Ethical Considerations). If the milk is allowed to be refed to the infant, the amount taken for assay should not deprive the infant of his or her nutritionally required volume.

  - FDA recommends the use of an electric pump rather than hand expression because electric pumps are more efficient in milk extraction. However, *hospital grade* pumps are not necessary; modern personal electric pumps utilize the same technology and are less costly.

E. Measurement of Infant Milk Intake

Sponsors should consider the following for measuring infant milk intake during clinical lactation studies:

- While a 150 mL/kg/day estimated milk intake is a reasonable assumption to estimate daily infant dosage, greater volumes do occur in early infancy and often correlate to the time of most reported infant adverse drug events. Additional consideration should be given to estimates of infant risk based on a 200 mL/kg/day milk intake in early infancy.

- Measurement of milk volume and weighing infants before and after feeding are methods that provide milk volume data for use in calculating infant exposure.

F. Pharmacokinetic Analysis

Analytical methods should be adequately validated, including both blood and breast milk, to address the accuracy, precision, selectivity, sensitivity, reproducibility, and stability of the parent drug and active metabolites of pharmacological importance.[8]

- Milk pharmacokinetics
  - The area under the milk concentration-time curve (AUC) should be calculated.
  - Average concentration should be based on AUC derived from collections at multiple time points, not just concentrations obtained at one sampling time.
  - Total milk concentration data should be used to estimate PK parameters of the parent drug and metabolites.
  - Peak and trough milk concentrations, as well as time to reach peak milk concentration, should be reported.
- Plasma pharmacokinetics (for milk and plasma study)
  - In general, plasma PK parameter estimates can include the following:
    - Area under the plasma concentration curve
    - Peak plasma concentration
    - Time to peak plasma concentration
    - Plasma clearance or apparent oral clearance
    - Apparent volume of distribution
    - Terminal half-life
  - PK parameters should be expressed in terms of total and unbound concentrations. For drugs and metabolites with a relatively low extent of plasma protein binding, FDA recommends that sponsors describe and analyze the pharmacokinetics in terms of total concentrations.
  - FDA also recommends noncompartmental and/or compartmental modeling approaches to parameter estimation.

G. Estimation of Infant Dosage

Sponsors should consider the following for calculating or estimating infant dosage:

[8] See the guidance for industry *Bioanalytical Method Validation* (May 2018).

- The daily infant dosage (total drug present in milk and consumed by the infant per day) should be calculated or estimated. Sponsors should consider the following to calculate daily infant dosage:

  Daily Infant Dosage (mg/day) = Σ (total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection)

  or

  Estimated Daily Infant Dosage (mg/kg/day) = M/P multiplied by the average maternal plasma concentration multiplied by 150 mL/kg/day

  M/P is the milk-plasma ratio. The calculation of M/P should be based on AUC and on multiple time points over 24 hours and not just a single point in time. Sponsors should consider an estimate of infant risk based on a 200 mL/kg/day infant milk intake in early infancy.

- The relative infant dose (the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 hours) should be calculated. Sponsors should consider the following for relative infant dose:

  Relative Infant Dose = Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day) multiplied by 100

- If the drug has an approved indication for use in pediatric patients younger than 1 year of age, the estimated daily infant dosage should be compared to the approved dose. Calculation of the percentage of estimated daily infant dosage to the approved dose can provide an estimate of the risk to the infant.

- Infant pharmacokinetics (for a mother-infant pair study) should be considered. If infant drug concentration data are not collected, the average infant drug concentration ($C_{ss,ave}$) can be estimated by using the following formula:

  $C_{ss,ave}$ *= F multiplied by infant dosage/CL*

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

H. Infant Safety Data Collection

An important component of clinical lactation studies is the collection of safety information in the breastfed infant. Follow-up examination or testing of the infant to evaluate for adverse drug events may be considered depending on the specific risk profile of the drug. Adverse drug event data can also be collected about the infant from mothers through surveys conducted electronically, by phone, or through maternal diaries.

I. Data on Effect of Drug on Milk Production

The clinical lactation studies described in this guidance are not formally designed to assess the effect of a drug on milk production. However, a sponsor should consider assessments about the effect of the drug on milk production in clinical lactation studies. For example, clinical lactation studies may include reports from enrolled women of any effects on milk production and, when feasible, a comparison of milk production before (or after discontinuation of) treatment to milk production during treatment.