

Clinical Lactation Studies-

Study Design Data Analysis Labeling



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Questions and Answers

- What is a guidance?
- Why a guidance on clinical lactation studies?
- What are the important elements of the Draft Guidance on Clinical Lactation Studies?
- What questions were raised by the public comments?
- What questions would we like the AC members to consider today?

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What is a Guidance Document

- Guidance documents represent FDA's current thinking on a topic.
- They are not laws or regulations.
- They do not bind FDA or the public.
- A person or company can choose to use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.
- Guidances use the term “should” rather than “must.”

Why Guidance on Clinical Lactation Studies?

- FDA wants to provide industry with clear, comprehensive, scientifically sound guidance on how to acquire clinically useful data from clinical lactation studies.
- The information obtained from these studies will be included in drug product labeling to equip clinicians and pregnant and lactating patients with the facts they need to make well-informed risk/benefit decisions about breastfeeding and medicine use.
- The knowledge and expertise you share with us today through your discussions and deliberations will help us to achieve these goals.

Lactation Guidance Goals

- Define when data from clinical lactation studies would and would not offer clinically useful information
- Provide a basic framework for design, conduct, and analysis of clinical lactation studies
- Stimulate further study and research in rational therapeutics for lactating patients.

No substitute exists for specific knowledge

- It is equally inappropriate to discontinue breastfeeding when it is not medically necessary as it is to continue breastfeeding while taking contraindicated drugs.

Lawrence RA, Lawrence RM. Breastfeeding: A Guide for the Medical Professional
Chapter 11: Drugs in breast milk; Elsevier and Mosby; Philadelphia. 1999.

Breast milk:

**The most complete form of nutrition for infants
Offers a range of health benefits for women and
infants**

- 10% of women of reproductive age are pregnant at any one time
- Pregnant and breastfeeding women sometimes need medicines to treat ongoing medical conditions or acute medical problems
- It is important to determine when the benefits of breastfeeding outweigh the risks of drug exposure through milk and vice versa.

Nursing Mothers Use Medicines

- 90-99% receive a medicine during the first week postpartum (Hale, 2004; Ito and Lee, 2003; Bennett, 1988)
- 17-25% have used another medicine by four months postpartum (Bennett, 1988)
- 5% receive long term drug therapy (Bennett, 1988)
- Breastfeeding women use an average of 3 to 4 different medicines while breastfeeding (excluding dietary supplements). (Stultz et al 2007)
- About 2/3 of medicines used may be over-the-counter medicines. (Stultz et al 2007)

Breastfeeding Benefits and Goals

- Benefits of human breast milk feeding
 - Updated since publication of draft
- Healthy People 2010 Initiative: HHS Blueprint for Action on Breastfeeding
 - 75% mothers breastfeeding in immediate postpartum period
 - 50% breastfeeding 6 months postpartum
 - 25% breastfeeding 12 months postpartum

Data that can be obtained from clinical lactation studies

- Extent of drug transfer into milk; infant daily dose
 - What we most want to know
- Effect of drug on milk production
 - Challenging in situations where drug is used chronically
 - Most drugs known to affect milk supply are known to do so through the drug's mechanism of action and its relationship to breastfeeding physiology.

Data that can be obtained from clinical lactation studies

- Effect of lactation on maternal pharmacokinetics or pharmacodynamics
 - Pregnancy physiology affects drug pharmacokinetics
 - It is not clear whether lactation is associated with changes in drug pharmacokinetics or pharmacodynamics outside the normal range for adult women
- Frequency and severity of adverse effects in breastfed infants exposed to maternal drug through breast milk
 - Important but hard to detect with small sample sizes
 - Harder to detect if adverse effect doesn't manifest until a later age.
 - Hard to distinguish effects due to exposure in utero vs. through breast milk.

Draft Guidance: Sections for discussion

- Ethical Research in Mothers and Infants 
- Existing Non-Human Data
- Existing Human Data and Deciding When to Conduct a Clinical Lactation Study
- Study Design Considerations
- Data Analysis
- Labeling

Ethical Research in Mothers and Infants

- Draft Guidance did not contain an Ethics section
 - Some public comments noted absence of an ethics section
 - Some public comments implied a lack of awareness of ethical issues relevant to clinical lactation studies.
- Ethical Issues:
 - Protection of the infant as a research subject
 - Drug exposure
 - Blood draws
 - Interference with breastfeeding
 - Mothers who medically require medication
 - Mothers who are healthy volunteers
- Dr. Nelson will address this topic later this morning

Existing Non-Human Data

- At this time, in-vitro and animal studies have not been validated as surrogates for human testing for drug levels in breast milk
- Many comments questioned or criticized the statements in the Draft Guidance regarding in-vitro and animal study models.
- In the future, if an in-vitro or animal study model proves to be a reliable surrogate for human breast milk studies, FDA will update the Guidance.

Existing Human Data and When to Conduct a 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.”

Situations when clinical lactation studies should be done

- Original or supplemental drug reviews where drug use is expected in women of reproductive age
- Use of a drug by lactating women becomes evident following marketing approval (e.g. metoclopramide)
- Marketed medicines commonly used by women of childbearing potential (e.g. asthma medicines)

Examples of medicines commonly used in women of reproductive age

- Antidepressants
- Antipsychotics
- Antihypertensives
- Anti-infectives
- Asthma medications
- Oral hypoglycemics
- Analgesics
- Acid reducers
- Various OTC medicines

Situations when clinical lactation studies are likely not needed

- Drug is not used in lactating women or women of reproductive age
- Drug is not systemically available in the mother
- Drug is not expected to be orally bioavailable in the infant
- Well designed lactation studies in humans have already been done
- Drug is used to treat a medical condition where breastfeeding is not advised (e.g. HIV)
- Potentially, drugs known to interfere with normal growth

Study Designs

- The Draft Guidance presented three primary study designs:
 - Lactating women, milk only
 - Lactating women, plasma and milk
 - Mother-Infant pair designs
- Confusion and concern expressed through public comments suggested that information about the 3 study designs was not clear or well organized:
 - Should milk only studies always be done first?
 - When should one choose a maternal plasma/milk study or mother-infant pair design instead?
 - Are there situations where more than one of these studies would be needed for a particular drug?

Lactating Women, Milk Only

What we can learn:

- Concentrations of drug and active metabolites in milk:
 - C_{max} overestimates infant daily dose.
 - C_{av} provides a more accurate infant daily dose and can be estimated using either the rectangular AUC or trapezoidal rule
- Absolute oral infant daily dose

$$\text{Dose}_{abs} = C_{milk} \times V_{milk}$$

Dose_{abs} = absolute daily infant dose
 C_{milk} = drug concentration in milk (either C_{max} or C_{av})
 V_{milk} = volume of milk ingested in 24 hours.

- For milk volume, use average intake by infant weight (150 mL/kg/day for exclusively breast fed infant) or calculate from infant weight change pre- and post-feed

Lactating Women, Milk Only

More we can learn:

- Relative infant dosage (% maternal dosage)

$$\text{Relative infant dose (\%)} = \frac{\text{Absolute infant dose (mg/kg/day)}}{\text{Maternal dose (mg/kg/day)}} \times 100$$

- Milk fat content (creamatocrit)

Lactating women, plasma and milk

What we can learn:

- Milk/plasma ratio for the drug
 - Drug concentration in milk divided by drug concentration in maternal plasma.
- Use milk/plasma ratio to calculate estimated oral daily infant dose. This may be useful in specific situations:

$$\text{Dose}_{\text{est}} \text{ (mg/kg/d)} = \text{M/P} \times \text{mean maternal plasma concentration} \times 150 \text{ mL/kg/d}$$

- Maternal pharmacokinetics

Mother-Infant Pair Design

What we can learn:

- Infant plasma drug levels
 - Limited sampling
 - Lucky to get one sample; mothers may refuse
 - Identify “best” sampling time relative to maternal dosing
 - Total plasma drug concentrations
 - Sample volumes too small for total and unbound plasma levels
 - Can calculate systemic dose
 - Actual infant oral bioavailability of drug will probably never be known
- Descriptive infant adverse event collection?
 - Small sample size and short term assessment limit detection
- Possible clinical use of qualitative data from noninvasive pediatric sampling techniques (tears, saliva, urine)?

Other study design considerations

- Supporting mother/infant breastfeeding pairs
 - Participating in a clinical lactation study should not increase the chance that a mother/infant pair will fail breastfeeding
 - How and when to use strategies to minimize infant exposure (dose timing, pumping and discarding milk)
- Who should be enrolled?
 - How many weeks postpartum?
 - Exclusive breastfeeding only?
 - Therapeutic use of drug only...or a role for healthy volunteers?
- What are effective recruitment methods?
 - Use of a pregnancy registry population to enroll subjects in a clinical lactation study.

Other study design considerations

- How large a sample size?
 - Studies traditionally very small
 - Is there value in requiring sample size ≥ 30 ? Is this realistic?
- When (if ever) is a control population needed?
 - For PK, can one use historical populations of non-pregnant women from PK trials previously completed
 - For studies that assess milk production/composition, can one use lactating women not using drug of interest?
 - When are prospective control populations useful?

Other study design considerations

- Breast milk sampling techniques
 - Want to characterize the complete dosing interval
 - Complete emptying of the breasts with a double electric pump at several collection intervals over 24 hours
 - Representative milk samples at several points over dose interval
 - Equal volumes collected pre-and post-feed
- Identify clinical management strategies that minimize infant exposure to drug when the drug is used as a single dose or in a limited number of doses.
 - Timing of medicine dose based on infant feeding schedule
 - Limited pumping and discarding of milk based on drug pharmacokinetics.

Data Analysis

- Drug assay development and precision
 - Precision at comparable drug concentrations is lower for breast milk than plasma probably due to variable lipid content of breast milk
 - Examples of methods for assay development and validation:
 - Assay validation at extremes of milk composition
 - Construction of a standard assay curve from individual breast milk samples “spiked with drug” (Begg, 2002)
- Data may primarily use descriptive statistics
 - Assess the clinical impact of maternal drug on the mother and breastfeeding baby.
 - Identify ways to minimize infant drug exposure during breastfeeding

Labeling

- Currently “Nursing Mothers” section under “special populations”
- Draft Pregnancy Labeling Rule currently in clearance process
 - Addendum to the Physicians Labeling Rule (PLR) for the pregnancy and nursing mothers sections of labeling
 - Elements
 - Summary
 - Clinical considerations
 - Data

Other Issues Raised in Public Comments

- The Guidance implies that nearly all drugs could be potentially used in lactating women. Requiring lactation studies for all drugs that could be used is not practical and would create an unnecessary burden.
 - Question: Is it a burden that lactating women and their healthcare practitioners need to make medicine use decisions without adequate data to properly assess risk and benefit?
- Lactating women and infants should not be exposed to a NME until sufficient safety data have accumulated.
 - Question: How will we define sufficient data? Will this be drug dependent?

Other Issues Raised in Public Comments

- Vaccines
 - This document will address lactation studies with drug products and therapeutic biologics (regulated by CDER) but not vaccines.
 - Vaccines are regulated by the Center for Biologics Evaluation and Research (CBER)
- Radionucleotide products
 - There are data published on the radioactivity half lives of various diagnostic and therapeutic radionucleotides
 - Recommendations about continued breastfeeding and pumping and discarding milk should be driven by the product's radioactivity half life
 - Nuclear medicine groups advise patients that most radioactive tracers are undetectable within 24-48 hrs and that women may need to pump and discard milk during that time.
 - Guidelines for disposing of body fluids (like urine) should be used for pumped breast milk.

Questions for Advisory Committee

- 1) Would data from clinical lactation studies be useful to practitioners and pregnant and breastfeeding patients when making risk/benefit decisions regarding medicine use during breastfeeding?
- 2) FDA is seeking guidance from the Advisory Committee regarding timing of study enrollment for mother/infant pairs.
 - Is it important for breastfeeding to be well established before enrolling mother/infant pairs in clinical lactation studies?
 - Is there a minimum number of weeks postpartum before which mother/infant pairs should not be enrolled? Please consider both infant feeding issues and maternal physiology and pharmacokinetics issues.

Questions for Advisory Committee

- 3) Should clinical lactation studies only enroll mother/infant pairs who are exclusively breastfeeding?
 - If yes, explain why.
 - If no, describe study scenarios where enrollment of mother/infant pairs who not exclusively breastfeeding would be useful.
- 4) Given that estimated infant daily dose can be calculated from drug concentrations in breast milk, are there situations where a maternal milk/plasma ratio would offer additional clinically useful information?

Questions for Advisory Committee

- 5) Based on drug characteristics or existing clinical concerns, are there situations when a mother/infant pair study with infant plasma sampling should be recommended?
 - Are there situations when a mother-infant pair study should be conducted without a prior milk-only or milk/plasma study? Please describe.

Questions for Advisory Committee

- 6) Are there any situations where it is appropriate to enroll healthy volunteers in clinical lactation studies?
 - Please consider: single versus multiple dose studies, ongoing breastfeeding versus weaning, and continued nursing during drug administration versus pumping and discarding milk
 - If no, explain why
 - If yes, describe the acceptable situations.
- 7) When in the drug regulatory process should clinical lactation studies be requested and done?

Clinical Pharmacology Considerations for Conducting Lactation Studies

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Considerations in Evaluating Drug Transfer Into Breast Milk

- Is the drug systemically available?
- Is the drug excreted into breast milk?
- If so, what amount of drug is excreted into breast milk?
- What percent of the maternal dose (pediatric dose, if applicable) is excreted into breast milk?

Considerations in Evaluating Drug Transfer Into Breast Milk

- Is the drug absorbed by the infant?
- If so, what is the infant exposure relative to the maternal exposure?
- What is the benefit of calculating the milk/plasma (M/P) ratio in addition to determining the amount of drug excreted into breast milk?
- Should the M/P ratio be used to assess drug excretion into breast milk for new formulations or dosage regimens?

Milk-Only Study

- Mother only – No additional risk to infant
- Provides the amount of drug excreted into breast milk
- Able to assess a drug's impact on milk production and composition

Milk-Only Study Considerations

- Should this always be the first study performed?
- Useful for short-term and chronic therapy
- Assesses excretion of drug into breast milk prior to performing a mother/infant study
- Allows determination of the daily infant dose

Milk-Plasma Study

- Mother only – No additional risk to infant
- Provides all data from milk-only study
- Additional assessment of plasma concentration-time profile
- Allows calculation of the milk-plasma (M/P) ratio

Milk-Plasma Study Considerations

- May be useful in the following situations:
 - Short-term therapy
 - Drugs known or likely to be excreted into breast milk
 - Drugs with narrow safety margins

Mother-Infant Study

- Provides all data from milk-plasma study
- Can address whether a drug is absorbed by the infant
- Allows calculation of infant exposure
- Allows assessment of drug's pharmacodynamic effect in infant

Mother-Infant Study Considerations

- May be useful in the following situations:
 - Chronic therapy
 - Drugs with high oral bioavailability
 - Drugs or metabolites with long half-lives
 - Drugs likely to accumulate in infant
- Collection of urine from infant to confirm lack of drug absorption

Potential knowns and unknowns drug in infant

- | | |
|--|--|
| <ul style="list-style-type: none">■ Knowns<ul style="list-style-type: none">■ Maternal plasma and breast milk concentration■ Ingested dose■ Infant plasma concentration■ Presence or absence of drug in urine or other fluid■ Oral clearance | <ul style="list-style-type: none">■ Unknowns<ul style="list-style-type: none">■ Oral bioavailability■ Actual dose absorbed from gut■ Renal clearance of drug |
|--|--|

Study Designs to Assess Effects of Lactation on Maternal Pharmacokinetics

Study Designs

- Longitudinal design
 - Same subjects sampled multiple times during the course of breastfeeding (at different infant ages)
 - Chronic use drugs; drugs given for several cycles
 - Decreases inter-individual variability
 - With or without infant sampling
- Multiple arm design
 - Enroll women of different ages and sample during breastfeeding and after weaning
 - Pair samples for analysis
 - Single use/short course drugs
 - With or without infant sampling

Longitudinal Design and Multiple-Arm Design Studies

- What are the benefits of performing these studies?
- When should these studies be performed in relation to the onset of breastfeeding?