
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DRAFT GUIDANCE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)**

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 meeting³ 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considered how data from clinical lactation studies can inform the safety of a drug when used during lactation.⁵ This draft guidance replaces the draft guidance for industry *Clinical Lactation Studies — Study Design, Data Analysis, and Recommendations for Labeling*, which published in February 2005.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.

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35 addressed in 21 CFR 201.57(c)(9)(ii) and the draft guidance for industry *Pregnancy, Lactation,*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

38
39 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
40 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
41 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
42 the word *should* in Agency guidances means that something is suggested or recommended, but
43 not required.

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II. BACKGROUND

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

56

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

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III. CONSIDERATIONS FOR CLINICAL LACTATION STUDIES

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A. Considerations for Conduct of a Clinical Lactation Study

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

72

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

77

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>.

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- 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)

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

90

B. Ethical Considerations

92

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

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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.

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- 120 • It is acceptable to enroll breastfeeding women who are participating in a clinical trial
121 of an investigational drug in clinical lactation studies if the breastfeeding woman
122 agrees to temporarily pump and discard milk to avoid exposing an infant to the
123 investigational drug. The length of time that the milk will need to be discarded
124 should be specified in the protocol and will vary depending on factors such as the
125 half-life of the drug.
126
- 127 3. Women who are healthy volunteers and are administered the investigational drug for the
128 purpose of clinical research
129
- 130 • In a research setting where a healthy woman who is currently breastfeeding
131 volunteers for a clinical lactation study, breastfeeding must be discontinued for the
132 duration of the study so that an infant is not exposed to the investigational drug.
133

C. Study Design Considerations

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135
136 In considering the appropriate type of clinical lactation study to conduct, the sponsor should
137 consider strategies that minimize the burden of data collection on the mother while obtaining
138 adequate data. The study should avoid disruption of the breastfeeding routine and support return
139 to breastfeeding if breastfeeding must be temporarily discontinued. Additionally, use of remote
140 clinical study sites may provide access to a patient population that may not otherwise be willing
141 or able to participate. Home health care nursing visits can be particularly important to successful
142 recruitment and conduct of lactation studies of drugs with longer half-lives, when many visits
143 occur over a period of several weeks.
144

1. General Study Designs

145
146
147 Sponsors should consider the following types of study designs for clinical lactation studies:
148

- 149 • Lactating woman (milk-only) study
150
- 151 – A milk-only study can be used to detect the presence of a drug in breast milk,
152 quantify or estimate the total amount of a drug transferred into breast milk (when
153 plasma concentrations are known), and evaluate the effects of a drug on milk
154 production (when milk production in lactating women not taking the drug is known).
155 If the concentration of a drug in breast milk is found to be clinically relevant, this
156 finding could lead to further studies.
157
- 158 – In general, FDA recommends milk-only studies unless there is a reason to conduct
159 another type of clinical lactation study.
160
- 161 • Lactating woman (milk and plasma) study
162
- 163 – Milk and plasma collection in lactating women can provide pharmacokinetic (PK)
164 data on a drug in a lactating woman, the amount of drug transferred into breast milk,
165 and the effects of a drug on milk production. In certain situations, the PK data of the

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

- 169
- 170 • Mother-infant pair study
 - 171
 - 172 – Mother-infant pair studies that include assessment of drug concentrations in infants
173 can provide information on absorption of drugs in infants through breast milk and
174 safety assessments in infants enrolled in these studies. A sponsor should consider this
175 design if information is already available about the extent of drug transfer into breast
176 milk including evidence that the drug accumulates in breast milk and if the drug is
177 likely to be absorbed by the breastfed infant.
 - 178

179 2. *Other Study Design Considerations*

180

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

- 183
- 184 • Single-dose design
 - 185
 - 186 – For drugs that are given acutely (e.g., single-dose drug, drugs that do not accumulate
187 with chronic dosing), a single-dose study may be sufficient.
 - 188
 - 189 • Longitudinal design
 - 190
 - 191 – For drugs that are administered chronically or given for several treatment cycles, a
192 sponsor may consider a longitudinal study design. Under such a design, samples are
193 obtained from each lactating woman at different time points (e.g., at 2–3 months and
194 then again at 5–6 months).
 - 195
 - 196 • Multiple-arm design
 - 197
 - 198 – For drugs that are given acutely (e.g., single dose or short course of therapy), a
199 multiple-arm study can be used to compare different lactating patients at different
200 postpartum times. Under such a study, samples are obtained from different lactating
201 women at different time points (e.g., at 2–3 months, 5–6 months).
 - 202

203 3. *Study Subject Considerations*

204

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

- 207
- 208 • Maternal factors
 - 209

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- 210 – Maternal weight, age, gestational age at delivery, stage of lactation, length of time
211 postpartum, smoking, alcohol intake, concomitant drugs, ethnicity, race, and existing
212 medical conditions should be collected and reported for each study subject.
213
- 214 – The study should specify subjects who exclusively breastfeed versus those who
215 supplement with infant formula. Although FDA recommends that studies include
216 only women who exclusively breastfeed, including women who are supplementing
217 with infant formula provides *real life* data and may allow for easy collection of
218 pumped milk that would otherwise be discarded. However, studies should report the
219 extent of use of infant formula.
220
- 221 • Infant factors (for infants enrolled in mother-infant pair studies)
222
 - 223 – Age, weight, history of prematurity, drugs, existing medical conditions, ethnicity, and
224 race should be collected and reported for each infant enrolled in a mother-infant pair
225 study.
226

4. *Sample Size Considerations*

227
228
229 Sponsors should consider the following for sample sizes in clinical lactation studies:
230

- 231 • Sample size considerations include PK variability for the drug being studied, the study
232 design (i.e., single dose versus multiple dose), and the variability in lactation physiology.
233
- 234 • A sponsor should consider the inter- and intra-subject variability for both mother and
235 breastfed infant, depending on the design and primary objective of the study. For
236 example, an increase to the sample size may be warranted if there is evidence of high
237 inter- or intra-subject variability.
238

D. Milk Sampling Methods

239
240
241 For milk sampling during clinical lactation studies, sponsors should consider the following:
242

- 243 • Type of milk collected
244
- 245 – The study design should specify the type of milk to be collected. For example,
246 differences in composition of foremilk versus hindmilk should be accounted for with
247 some drugs because transfer of drugs may be affected by the composition of the milk
248 (e.g., foremilk contains more water and less fat which may affect the transfer of
249 lipophilic drugs).
250
- 251 – Sampling should ideally take place after the development of mature milk (after
252 approximately 10 days postpartum). Colostrum or transitional milk collection may
253 not reflect drug transfer in mature milk because drug transfer may be transiently
254 increased because of a more porous mammary epithelium. However, sampling of
255 colostrum or transitional milk may be important under certain circumstances. For

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

258
259 – The specific timing of the milk sample relative to both the dose and days postpartum
260 should routinely be collected.

261

262 • Milk sampling method

263

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

272

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

278

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

283

284 **E. Measurement of Infant Milk Intake**

285

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

288

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

293

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

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297 **F. Pharmacokinetic Analysis**

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

- 302
- 303 • Milk pharmacokinetics
 - 304 – The area under the milk concentration-time curve (AUC) should be calculated.
 - 305
 - 306 – Average concentration should be based on AUC derived from collections at multiple
 - 307 time points, not just concentrations obtained at one sampling time.
 - 308
 - 309 – Total milk concentration data should be used to estimate PK parameters of the parent
 - 310 drug and metabolites.
 - 311
 - 312 – Peak and trough milk concentrations, as well as time to reach peak milk
 - 313 concentration, should be reported.
 - 314
 - 315 • Plasma pharmacokinetics (for milk and plasma study)
 - 316 – In general, plasma PK parameter estimates can include the following:
 - 317
 - 318
 - 319
 - 320 ▪ Area under the plasma concentration curve
 - 321 ▪ Peak plasma concentration
 - 322 ▪ Time to peak plasma concentration
 - 323 ▪ Plasma clearance or apparent oral clearance
 - 324 ▪ Apparent volume of distribution
 - 325 ▪ Terminal half-life
 - 326
 - 327 – PK parameters should be expressed in terms of total and unbound concentrations. For
 - 328 drugs and metabolites with a relatively low extent of plasma protein binding, FDA
 - 329 recommends that sponsors describe and analyze the pharmacokinetics in terms of
 - 330 total concentrations.
 - 331
 - 332 – FDA also recommends noncompartmental and/or compartmental modeling
 - 333 approaches to parameter estimation.
 - 334

335 **G. Estimation of Infant Dosage**

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337 Sponsors should consider the following for calculating or estimating infant dosage:
338

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

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- 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:

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

345

346 or

347

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

350

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

- 355
- 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:

356

357

358

359

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

- 362
- 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.

- 363
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- 366
- 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:

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368

369

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371

372 $C_{ss,ave} = F$ multiplied by infant dosage/CL

373

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

H. Infant Safety Data Collection

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377

378

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

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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.