
Postapproval Pregnancy Safety Studies 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DRAFT GUIDANCE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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Postapproval Pregnancy Safety Studies Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to provide sponsors² and investigators with recommendations on how to design investigations to assess the outcomes of pregnancies in women exposed to drugs and biological products regulated by FDA (i.e., pregnancy safety studies). The goal of postapproval pregnancy safety studies is to provide clinically relevant human safety data that can inform health care providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of drugs and biological products through inclusion of the information in a product's labeling.

In the years since FDA issued guidance on this topic, pregnancy safety studies required by FDA have expanded beyond those using data from pregnancy exposure registries (pregnancy registries)³ to also include other types of epidemiologic studies and pregnancy surveillance programs. This guidance should be used in conjunction with other epidemiological literature on the design, conduct, and interpretation of observational studies. The development of pregnancy safety studies requires specialized knowledge in a variety of areas, including expertise in the fields of epidemiology, clinical teratology, obstetrics, pediatrics, clinical genetics, and statistics when designing a study.⁴

¹ This guidance has been prepared by the Postapproval Pregnancy Safety Studies working group in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Women's Health in the Office of the Commissioner at the Food and Drug Administration.

² For the purposes of this guidance, *sponsors* refer to persons or entities that conduct or fund studies for approved products.

³ A pregnancy registry collects data that are then analyzed to address a safety question. For the purposes of this guidance, *pregnancy registry* refers to both the data collection and the study that uses the data.

⁴ The previous guidance for industry *Establishing Pregnancy Exposure Registries* published August 23, 2002, has been withdrawn.

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

40

41

II. BACKGROUND

42

43
44 Pregnant women represent an important segment of the population, with over 6 million
45 pregnancies occurring per year, based on national vital statistics (Curtin et al. 2015). Pregnant
46 women may have chronic conditions, such as diabetes, seizure disorders, or asthma, that need to
47 be treated during pregnancy, or pregnant women may develop acute or serious medical
48 conditions during pregnancy that require treatment. In addition, nearly half of all pregnancies in
49 the United States may be unintended, which could result in potential inadvertent exposure to
50 drugs and biological products in pregnancy if a woman is exposed to a drug when she is not
51 aware she is pregnant (Finer 2016). Therefore, there is an important need for safety information
52 on product exposure during pregnancy.

53

54 During clinical development of most drugs and biological products, pregnant women are actively
55 excluded from trials, and if pregnancy does occur during a trial, the usual procedure is to
56 discontinue treatment and monitor the women to assess pregnancy outcomes. Consequently, at
57 the time of a drug or biological product’s initial marketing, except for drugs and biological
58 products developed to treat conditions unique to pregnancy, there are no or limited human data to
59 inform the safety of a drug or biological product taken during pregnancy.

60

61 Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C.
62 355(o)(3)), added by section 901 of the Food and Drug Administration Amendments Act of 2007
63 authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs
64 approved under section 505(b) of the FD&C Act and biological products approved under section
65 351 of the Public Health Service Act (42 U.S.C. 262). Under section 505(o)(3), FDA can require
66 such studies or trials at the time of approval to assess a known serious risk related to the use of
67 the drug, to assess a signal of serious risk related to the use of the drug, or to identify an
68 unexpected serious risk when available data indicates the potential for a serious risk. Under
69 section 505(o)(3), FDA can also require such studies or trials after approval if FDA becomes
70 aware of *new safety information*.⁵ Postapproval studies using data collected in pregnancy
71 registries may be required to assess potential serious risks to the pregnancy that may affect the
72 health of the fetus or the woman due to drug or biological product use during pregnancy.⁶

73 However, gaps in safety data in pregnant women still exist.

⁵ Defined at section 505-1(b)(3) of the FD&C Act. Also see the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁶ See the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

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75 FDA held a 2-day public meeting in 2014 where stakeholders, including birth defect experts
76 from academia, industry, professional organizations, and patient groups, discussed the conduct of
77 pregnancy registries and epidemiologic studies using different study designs.⁷ In addition, FDA
78 conducted reviews of pregnancy registries listed on the FDA’s Office of Women’s Health web
79 page (Gelperin et al. 2017). Based on FDA reviews and the 2014 public meeting, FDA
80 understands that pregnancy registry data have contributed to labeling changes and clinical
81 guidelines, but their potential has not been fully realized, often because of feasibility issues.

82
83 Pregnancy registries remain an important tool for safety data collection in the postmarketing
84 setting because of the prospective design and the ability to collect detailed patient level data.
85 However, because of the recurring challenges of achieving sufficient enrollment, pregnancy
86 registries generally are not sufficient by themselves to assess the safety of products during
87 pregnancy; therefore, other study methods capable of appropriately assessing the occurrence of
88 specific major congenital malformations (MCMs) (e.g., birth defects and congenital anomalies)⁸
89 and other pregnancy outcomes are needed. In addition, use of complementary approaches may
90 help address the limitations inherent to a specific study design and provide greater confidence in
91 the conclusions. Input received from the 2014 public meeting and findings from FDA reviews
92 were used to develop this guidance.

93
94 The following sections describe three general approaches (pharmacovigilance, pregnancy
95 registries, and complementary data sources) that can be used in the postmarket setting to evaluate
96 drug or biological product safety during pregnancy. These approaches are not intended to imply
97 a hierarchy of evidence from the different study methods. Rather, each approach may uniquely
98 contribute to the overall safety assessment of a product during pregnancy. When considering
99 postmarketing approaches, the selection of any one or combination of these assessments and
100 timing of initiation may vary by drug or biological product. Consideration can be given to
101 experience with similar drugs and biological products, knowledge of the underlying disease and
102 its risks (maternal and fetal), potential use of the drug or biological product in females of
103 reproductive potential and pregnant women, existing knowledge of a safety concern, and the
104 potential for capturing the same pregnancy in two different assessments (*double counting*).
105 Moreover, evaluation of the strengths and limitations inherent to each type of assessment allows
106 FDA to recommend or require the appropriate method of postapproval risk assessment.⁹
107

⁷ See transcripts from the FDA public meeting “Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting,” May 28-29, 2014, at <https://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>.

⁸ For the purposes of this guidance, the following terms are used interchangeably: *congenital malformations*, *congenital anomalies*, and *birth defects*, and are referred to as MCM throughout this guidance.

⁹ The authority to require a responsible person to conduct a postapproval study or studies or clinical trial(s) of a drug under section 505(o)(3) includes the authority for FDA to set parameters for the study or trial to be conducted, including how the study or trial is to be done and the population and indication. In other words, under section 505(o)(3), we can require a study or clinical trial that is well designed and adequate to address the serious safety concern. Our current thinking on this and other matters is set forth in the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

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III. PHARMACOVIGILANCE — CASE REPORTS AND CASE SERIES

Good pharmacovigilance practice involves the collection of comprehensive data on adverse pregnancy outcomes to detect safety signals and develop a case series for analysis. Sources can include spontaneous reports submitted to the sponsor and FDA, as well as case reports from the medical literature or clinical studies. Well-documented and informative case reports can be used to identify a signal, particularly if the pregnancy outcome is rare in the absence of drug exposure. Safety signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the outcome or increased the risk of the outcome. The importance of astute clinicians and clinical judgment in identifying a distinctive and unique pattern of congenital malformations associated with a particular pregnancy exposure has been critical in identifying teratogens (Shepard 1994; Obican and Scialli 2011). The quality of the reports is critical for appropriate evaluation of the potential relationship between the product and adverse outcomes. FDA recommends that sponsors make a reasonable effort to obtain complete information for case assessment during initial contacts and subsequent follow-up.

Case reports are the most common source of reports of adverse pregnancy outcomes but can often be challenging to interpret because information is often incomplete or there are additional risk factors for the adverse pregnancy outcome, which case reports may not address. In addition, one needs to consider the background rates of adverse pregnancy outcomes. Good case reports include numerous important elements for conducting adequate pharmacovigilance. Specific critical factors in evaluating the effects of product exposure in human pregnancies may include, but are not limited to, the following:¹⁰

- A detailed description of the adverse pregnancy outcome
- A detailed description of the exposure including the specific medication, the dose, frequency, route of administration, and duration
- The timing of the exposure in relation to the gestational age
- The maternal age, medical and pregnancy history, and use of concomitant medications, supplements, and other substances
- Exposures to known or suspected environmental teratogens

FDA has occasionally considered case reports and case series to be adequate data sources for establishing a causal association for a human teratogenic exposure, such as with isotretinoin (Centers for Disease Control and Prevention (CDC) 1984; Rosa 1983), or a serious adverse event, such as oligohydramnios with trastuzumab (Zagouri et al. 2013). In general, such evidence has been evaluated on a case-by-case basis. Case reports have been most useful and influential in situations where the adverse pregnancy outcome rarely occurs as a background

¹⁰ See the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005).

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151 event, and the adverse outcome is well-documented. A suspected safety signal arising from case
152 reports and case series that is not initially confirmed should be viewed as the start of an iterative
153 process, and not necessarily conclusive evidence of absence of risk.

154
155 Known limitations of spontaneous postmarketing reports (such as under-reporting, lack of a
156 denominator, and incomplete information) pose considerable challenges in analyzing cases and
157 determining whether a causal relationship exists between a product exposure and an adverse
158 pregnancy outcome.¹¹ Thus, routine pharmacovigilance usually will be insufficient for a
159 conclusive assessment regarding the potential risk of an exposure during pregnancy because of
160 the inability to quantify risk. Observational studies such as pregnancy registries and other
161 pharmacoepidemiological studies usually are needed to provide additional information including
162 a control group to derive and compare rates on safety outcomes of drugs and biological products
163 used during pregnancy. A sponsor should have a structured approach for pregnancy surveillance
164 with targeted questionnaires to obtain follow-up information on all potentially exposed
165 pregnancies of which the sponsor becomes aware, regardless of whether the pregnant woman
166 chooses to enroll in a registry. Pregnant women should be able to decline participation or
167 additional follow-up at any time at their discretion.

168

169

170 **IV. PREGNANCY REGISTRIES**

171

172 **A. Overview**

173

174 A pregnancy registry actively collects information on drug or biological product exposure during
175 pregnancy and associated pregnancy outcomes, which can be used to conduct a prospective
176 observational study (women are enrolled before the pregnancy outcome). Pregnancy registries
177 depend on the voluntary participation of women who have been exposed to a specific drug or
178 biological product during pregnancy and unexposed women who enroll into the comparator
179 cohort. Pregnancy registry data are prospectively collected by maternal interview and medical
180 record documentation and may include results of the clinical examination of the newborn.
181 Because of the prospective design of pregnancy registries, they may support assessment of
182 multiple maternal, obstetrical, fetal, and infant outcomes, including pregnancies that do not result
183 in a live birth.

184

185 A pregnancy registry may be U.S.-based or international in its scope. When submitting interim
186 and final pregnancy registry study reports, sponsors should include cumulative analyses of
187 worldwide pregnancy surveillance data to provide perspective on registry feasibility and updates
188 on available safety data in pregnant women that may not be included in the registry.

189

190 Pregnancy registries have the following strengths:

191

- 192 • By enrolling women exposed to the product of interest, pregnancy registries can be an
193 efficient way to collect data on the effects of rare exposures during pregnancy.

194

¹¹ Ibid.

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- 195 • A pregnancy registry can be initiated and start to accrue real-time data as soon as a
196 product becomes commercially available, in contrast to the use of claims data and
197 electronic health records where there will be a lag time in data availability.
198
- 199 • Prospective enrollment facilitates ascertainment of an exposure of interest close to the
200 time it occurs and before information about the pregnancy outcome is known.
201
- 202 • Pregnancy registries have the potential to obtain accurate information about whether
203 exposure occurred and the timing of the exposure in relation to gestational age, dose,
204 frequency, and duration of the exposure, as well as covariates, and may therefore reduce
205 exposure misclassification, recall bias, and confounding.
206
- 207 • A pregnancy registry can potentially collect data on a variety of pregnancy and infant
208 outcomes, including postnatal outcomes.
209
- 210 • A pregnancy registry can be designed to include data from physical examination of the
211 newborn, and periodic clinical assessment of the offspring of exposed mothers, enabling
212 access to detailed clinical information about outcomes of interest, without relying on
213 International Classification of Diseases (ICD) codes.
214

215 Pregnancy registries have the following limitations:

- 216 • Analyses of collected data may have minimal statistical power to detect associations for
217 rare pregnancy outcomes.
218
- 219 • Most pregnancy registries are designed primarily to collect data used to assess the overall
220 risk of MCMs. Effects on less common, specific MCMs may be missed for all but the
221 most potent teratogens.
222
- 223 • Patient recruitment and retention are often challenging, and identification of an
224 appropriate comparator group may not always be feasible.
225
- 226 • Data from pregnancy registries generally are not sufficient by themselves to assess the
227 safety of products during pregnancy, and other study methods such as retrospective
228 cohort studies or case control studies may be needed to corroborate registry findings.
229

230
231 The ability of a pregnancy registry to provide safety data that can be used to inform product
232 labeling depends on factors such as the availability and quality of key clinical data and the
233 number of patients enrolled into the registry. Sponsors should address registry design
234 considerations (discussed below) in a written protocol and statistical analysis plan that include
235 considerations of study feasibility.
236

B. Registry Design Considerations

237
238
239 A well-written protocol for a pregnancy registry should describe its objectives, which may range
240 from open-ended safety surveillance to testing a specific hypothesis. The following issues

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241 should be addressed in the protocol to ensure consistency of data collection and analysis that will
242 provide scientifically valid results.

243

244 1. *Objectives*

245

246 The protocol should state the objectives of the registry for all study outcomes. An effective
247 pregnancy registry has the potential to serve as an early warning system to identify a previously
248 unrecognized major teratogen soon after market introduction by identifying MCMs in infants of
249 exposed mothers. For less potent teratogens or for drugs and biological products that cause other
250 adverse pregnancy outcomes, a pregnancy registry can function as a signal detection study and
251 generate hypotheses that can be tested using other methods that may be better powered to assess
252 specific birth defects or other abnormalities.

253

254 2. *Study Population for Inclusion*

255

256 Ideally, women in the exposed and unexposed cohort should be enrolled in a pregnancy registry
257 prospectively (i.e., before the conduct of any prenatal tests that could provide knowledge of the
258 outcome of pregnancy). If the condition of the fetus has already been assessed through prenatal
259 testing (e.g., targeted ultrasound, amniocentesis), such reports traditionally have been considered
260 retrospective. However, because it may be difficult to obtain enrollment before prenatal testing
261 on a consistent basis, the study population should include all women, including those who have
262 had early prenatal testing, and the protocol should address how pregnancies with prenatal testing
263 before enrollment will be evaluated in statistical analyses to avoid potential bias.

264

265 3. *Outcome Definition(s) and Ascertainment*

266

267 A pregnancy can result in live birth, miscarriage (loss before 20 weeks), elective termination, or
268 fetal death/stillbirth (loss after 20 weeks). Within each of these categories the fetus or infant can
269 be evaluated for the presence or absence of the primary outcome. As part of the study design,
270 the protocol should state a priori criteria for defining study outcomes. Criteria for defining birth
271 defects as *major* should be clearly stated. For example, MCMs might be defined as
272 “abnormalities in structural development that are medically or cosmetically significant, are
273 present at birth, and persist in postnatal life unless or until repaired.” Similarly, criteria should
274 be established for abnormalities that will be excluded from the definition of outcome (e.g., those
275 that are minor, transient, chromosomal abnormalities, genetic syndromes, positional defects,
276 prematurity related) (Holmes and Westgate 2011). A standardized classification system should
277 be used, as appropriate. An expert clinical geneticist or dysmorphologist should review and
278 classify medical records and reports of all MCMs. The clinical expert reviewer and method of
279 assessment should be the same for both the exposed and comparator group(s) and the reviewer
280 should be blinded to the exposure status.

281

282 Some examples of other outcomes that may be primary or secondary on a case-by-case basis
283 include:

284

- 285 • Measures of fetal growth deficiency (small for gestational age)
- 286 • Preterm delivery

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- 287 • Other pregnancy complications
- 288 • Developmental milestones or neurologic abnormalities in offspring of exposed mothers
- 289 • Abnormalities of immune system development in offspring of exposed mothers

290

291 4. *Sample Size and Statistical Power*

292

293 A written protocol for a pregnancy registry should include a statistical analysis plan with a
294 description of target sample size based on power calculations, and assessment of feasibility of
295 the study in the patient population of interest. When estimating the target sample size, it is
296 important to take into consideration the expected background rate of pregnancy loss, and cases
297 that may be lost to follow-up or otherwise unevaluable. Estimated rates based on the general
298 population may not apply to specific disease groups (e.g., diabetes).

299

300 Determination of an adequate sample size depends on the objective(s) and design of the registry
301 and the background rate of the outcome in the study population. If more than one pregnancy
302 outcome is considered, sample size determination should be based on the outcome with the
303 lowest background rate (e.g., MCMs). Consideration should be given to the prevalence of the
304 disease in females of reproductive potential and pregnant women and anticipated frequency of
305 product exposure in pregnant women.

306

307 No known teratogen increases the risk of all MCMs. Typically, a specific defect or pattern of
308 defects is associated with a specific teratogenic exposure during a critical period. Specific
309 MCMs occur rarely in the general population (i.e., fewer than 1 in 1,000 live births).

310 Historically, pregnancy registries have not had sufficient sample size or power to evaluate
311 increased risks for specific MCMs unless the relative risks are large (Gelperin 2017; Bird et al.
312 2018). Therefore, most registries compare the overall proportion of the total combined number
313 of various MCMs observed in the exposed group to the overall proportion in the comparator
314 group(s). Sponsors should include justification for the choice of expected background rates for
315 outcomes of interest in their proposed sample size and power calculations.

316

317 5. *Safety Evaluation When a Pregnancy Registry Is Not Feasible*

318

319 In some situations, a pregnancy registry may never have adequate power to allow statistical
320 inference. Achievement of an adequate sample size may not occur when the likelihood of
321 exposure in pregnancy is low, or use of a product is not recommended during pregnancy.
322 Anticipated issues with registry study feasibility should be stated in the protocol and
323 appropriately addressed, for example by expanding the inclusion criteria to include all reports of
324 exposed pregnancies (both prospective and retrospective). For products that are anticipated to be
325 used rarely during pregnancy (e.g., treatment of advanced cancer), sponsors can consider a
326 pregnancy surveillance program (a structured approach for data collection with targeted
327 questionnaires to obtain follow-up information on all exposed pregnancies of which sponsors
328 become aware). This type of case series of exposed pregnancies can inform clinical and
329 regulatory decision-making. Worldwide safety data collection is usually needed to identify a
330 sufficient number of exposed pregnancies for clinical safety assessment.

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6. Comparator Selection — Reference Group(s)

The strategy for selection of an appropriate comparison group(s) should be made when designing the pregnancy registry and should be included in the protocol. Ideally, the registry should enroll a concurrent internal comparison group of pregnant women unexposed to the evaluated treatment. In addition, patients with the same disease (and disease severity, if feasible) should be compared, because confounding due to the underlying condition may arise. Cohorts exposed to different treatment regimens, when available, can serve as additional internal comparator groups when evaluating a specific drug or biological product used as one treatment in a multiproduct or disease-based registry study (for example, autoimmune diseases).

A background rate or the prevalence of congenital anomalies in a population-based surveillance system (e.g., Metropolitan Atlanta Congenital Defects Program (MACDP))¹² or from another pregnancy registry may be the only available comparator in certain situations. However, if background rates or information from the external population-based surveillance system are chosen as a comparison group, it is important to be aware of the limitations of whatever existing system is used so that appropriate analyses can be designed, and results interpreted correctly. For example, while MACDP prevalence data are well-documented and stable over time, they have several characteristics that limit their validity as a comparator group for a pregnancy registry. Limitations include the small geographic region from which the data are drawn (metropolitan Atlanta); inclusion and exclusion criteria for outcomes of interest that differ from the registries (particularly with regard to chromosome abnormalities); and the duration of postnatal follow-up. Importantly, because external comparators typically estimate risk in the general, mostly healthy, population, they may not be helpful to discern effects of the exposure of interest and the underlying disease of the pregnant woman undergoing treatment, such as diabetes or asthma.

When available and feasible, sponsors can consider use of external databases with data on background rates in the disease population of interest to ensure comparability of groups. Selection of an appropriate comparator is important because comparing dissimilar populations could bias the study results, indicate a risk when none exists, or mask an increased risk that exists. When feasible, selection of multiple comparator groups may be informative.

7. Exposure Definition and Ascertainment

Sponsors should collect detailed information on start and stop dates for all products taken during pregnancy, as well as dose, frequency, duration, and indication. Exposure information in the time period just before pregnancy is also often important, especially for products with a long half-life. Accurate information about specific gestational timing of exposure(s) can help identify critical exposure periods during gestation and biological plausibility for specific effects.

8. Covariates — Potential Confounders

Sponsors should consider the potential for confounding by indication, which makes it difficult to determine whether any observed effects are caused by the drug or biological product or the

¹² <https://www.cdc.gov/ncbddd/birthdefects/macdp.html>

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377 underlying disease. Data should be collected on the pregnant woman’s pertinent medical history,
378 current disease status, and overall management. Other potential confounders for which data
379 should be collected include, for example: socioeconomic status, maternal age, tobacco and
380 alcohol use, illegal drug use, maternal body mass index, folic acid and vitamin use during the
381 pregnancy, obstetrical history, medical history, family history of adverse pregnancy outcomes
382 including MCMs, and other relevant confounders (Caton 2012).

383

384 9. *Data Collection*

385

386 The value of the pregnancy registry depends on the accuracy and comprehensiveness of its data.
387 All data collection efforts should be identical among exposed and comparator study groups to
388 minimize bias.

389

390 The objective(s) of the registry should determine the type, extent, and length of patient follow-
391 up. The feasibility of obtaining reliable pregnancy and infant outcome information is a critical
392 consideration in pregnancy registry design. Although prenatal health care providers are a good
393 source of information on outcomes, such as miscarriage, elective terminations, live births, and
394 pregnancy complications, they are not a good resource for information on infant conditions not
395 readily diagnosed at or soon after birth. The infant’s health care provider is the best resource for
396 full information on the health status of the infant after birth. The protocol should also specify
397 inclusion of pertinent findings from postmortem examination of pregnancies with nonlive birth
398 outcomes to avoid bias due to under-ascertainment of major malformations (Holmes and
399 Westgate 2011).

400

401 The protocol should include a plan and rationale for follow-up contacts during and/or after
402 pregnancy. The follow-up contact should obtain details on the pregnancy course, outcome,
403 status of the infant, and any evidence of abnormalities.

404

405 See Appendix A for a list of recommended data elements to include when designing a pregnancy
406 registry.

407

408 10. *Data Analysis and Presentation*

409

410 Validation of cases should be performed through medical record review and adjudication of
411 outcomes by a clinical dysmorphologist or appropriate specialist for both the exposed and
412 comparator group(s).

413

414 Inferential statistics should be applied to test prespecified hypotheses regarding the potential
415 association between the exposure and the outcome(s) of interest.

416

417 Potential biases should be discussed, as well as possible methods for mitigation, if applicable.
418 Descriptive statistics are the primary approach for summarizing patient characteristics and
419 additional data from a pregnancy registry. Given the heterogeneous nature of data obtained in
420 pregnancy registries, there is no one format for data presentation that is applicable for all studies.
421 The choice of a final format depends on outcomes identified in the registry protocol,
422 unanticipated findings, and expert advice. We encourage sponsors to develop forms of data

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423 presentation and analysis that fully capture outcomes of concern within their particular registry.
424 Separate analyses should be performed for each pregnancy outcome (miscarriage, elective
425 termination, fetal death/stillbirth, live birth) and stratified by gestational timing of exposure (with
426 a separate analysis of first trimester exposures for MCMs). Additional analytical approaches
427 should be used to assess covariates and factors that may affect the study findings, such as
428 gestational timing of enrollment (Margulis et al. 2015).

429

11. Privacy and Human Subject Protection Issues

431

432 Sponsors should consider privacy (including data protection) and human subject protection
433 (including obtaining informed consent and institutional review board (IRB) oversight) when
434 designing a pregnancy registry and developing protocols for the subsequent use of the data from
435 the registry. FDA recommends that an IRB be consulted when developing a pregnancy registry
436 to ensure that the collection of data and all other procedures associated with the registry will
437 withstand scientific and ethical scrutiny.

438

439 Because pregnancy registries typically do not involve the administration of an investigational
440 product, there is not likely to be any foreseeable risk or harm to the pregnant woman, fetus, or
441 resulting child from participating in the registry other than risk associated with inappropriate
442 disclosure of identifiable private information. The patient should be requested to sign medical
443 record release forms to allow collection of the records from the health care provider(s) of the
444 mother and infant. Investigators are responsible for ensuring that any data releases are compliant
445 with the Health Insurance Portability and Accountability Act and that all research performed
446 complies with standards of privacy of individually identifiable health information.

447

448 If the registry involves the collection of information on the child after birth, either through a
449 physical examination or specimen collection, considerations should be given to 21 CFR part 50,
450 subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated
451 human subjects research).

452

12. Independent Data Monitoring Committee/Scientific Advisory Board

454

455 To ensure scientific integrity and appropriate patient protection, we encourage each registry to
456 have an independent data monitoring committee (or scientific advisory board) similar to those
457 used for clinical studies. Members of the committee could include experts in obstetrics,
458 embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, and any
459 relevant therapeutic areas. The committee could assist in the review of data, classification of
460 specific pregnancy outcomes including MCMs when relevant, and the dissemination of
461 information to ensure that results are interpreted and reported accurately. We recommend that
462 the role and duties of the committee or scientific advisory board be specified in the protocol.

463

13. Recruitment and Retention Plans

465

466 Successful recruitment and retention strategies are critical to the success of pregnancy studies
467 such as registries or other studies requiring enrollment of study subjects. We recommend a
468 robust recruitment and retention plan that includes a multipronged approach to ensure

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469 widespread coverage of the eligible population. Early enrollment also may improve detection of
470 pregnancy outcomes such as miscarriage. These plans should be flexible and continuously
471 reassessed throughout the study to ensure the registry maintains an adequate number of eligible
472 pregnant women in both the exposure and comparator groups.

473
474 a. Recruitment

475
476 Engaging health care providers and patients before the initiation of recruitment increases
477 awareness of the study and provides an opportunity to seek feedback from these stakeholders
478 regarding the study plan. We encourage sponsors to collaborate with entities such as existing
479 registries, patient advocacy groups, medical societies, and other relevant organizations to engage
480 in awareness activities.

481
482 Under the Pregnancy and Lactation Labeling Rule requirements, if there is a pregnancy registry
483 for the product, relevant contact information must be included in product labeling under the
484 subheading Pregnancy Exposure Registry.¹³ Suggested modes of contact information include a
485 toll-free telephone number or a website's uniform resource locator (URL).

486
487 The FDA's Office of Women's Health (OWH) maintains an online list of pregnancy registries
488 that are actively enrolling women to raise awareness about pregnancy registries and connect
489 consumers and health professionals to registries. The registries are posted to the FDA's OWH
490 web page based on a sponsor's or investigator's request to list its registry. FDA encourages
491 sponsors and investigators to submit a pregnancy registry listing to OWH at
492 Registries@fda.hhs.gov. FDA does not endorse any registry and is not responsible for the
493 content of registries listed on the web page.¹⁴

494
495 Recruitment strategies can be described as facility-based, health care provider-initiated, or
496 patient-initiated.

- 497
- 498 • Facility-based recruitment can occur at the level of a practice or health system.
499 Electronic health records can be used to identify drug or biological product users to
500 facilitate the enrollment process for providers. For example, an automated alert of a
501 pregnancy registry can be generated in response to positive pregnancy test results and/or
502 specific drug or biological product prescriptions.
 - 503 • Health care provider-initiated recruitment of patients is an important deciding factor for
504 many pregnant women. Provider recruitment approaches include:
 - 505 – Announcement of the registry study and contact information in the product labeling
 - 506 – Promotional materials and product Internet pages
- 507
508

¹³ 21 CFR 201.57(c)(9)(i)(A).

¹⁴ The Pregnancy Registries web page is located at <https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm>. The OWH mailbox address and the web page URL may change. See the FDA website for the most recent information (<https://www.fda.gov/>).

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- 509 – Announcements in professional journals and newsletters
510 – Personal mailings to specialists
511 – Presentations and exhibits at professional meetings
512
513 • Patient-initiated recruitment efforts rely on patients to contact the registry study staff and
514 self-enroll. Because pregnancy is often recognized by the patient first, registries that
515 enroll patients directly can allow for recruitment of patients earlier in pregnancy. Useful
516 avenues to notify pregnant women of pregnancy registries include:
517
518 – Print media including publications, press releases, and articles in newspapers and
519 magazines with pregnant women among their readership
520
521 – Distribution of flyers and posters in locations such as hospitals, ultrasound clinics,
522 laboratories, prenatal classes, community centers, stores, and coffee shops (Webster
523 et al. 2012)
524
525 – Social media
526
527 – Downloadable applications for mobile devices or personal computers could enable
528 broader participation through ease of providing information¹⁵
529

530 Successful strategies to encourage the participation of pregnant women in medical research that
531 may be applicable to postapproval safety studies include:
532

- 533 • Incentives that facilitate study participation (Webb et al. 2010)
534
535 • Employing empathetic, culturally sensitive, and personable study staff (El-Khorazaty et
536 al. 2007).
537

b. Retention

538
539
540 Even though recruitment materials may yield strong initial recruitment results, we recommend
541 implementing a robust retention plan to ensure that an adequate number of pregnant women
542 remain in the registry. The retention plan should address specifics of patient retention strategies,
543 contingency plans to obtain follow-up information, methods to track follow-up rates over time,
544 and implementation steps to improve follow-up if expected follow-up rates are not met.
545

546 FDA also recommends that retention efforts focus on participating health care providers to
547 improve retention rates and reduce the burden of data collection (e.g., implementing streamlined
548 processes and succinct forms). Access to pregnancy registry results provides a strong incentive
549 for the participation of health care providers, particularly obstetric care providers, and the
550 provision of interim data reports to participating health care providers may bolster retention.
551 Additionally, high levels of retention have been achieved by pregnancy registries that
552 communicate directly with patients. Emphasizing the mission of the pregnancy registry may

¹⁵ See the FDA's MyStudies Application (App) web page at <https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm>.

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553 reinforce participants' motivation to remain in the study. Sharing study results through a
554 newsletter or website has been found to be effective in reinforcing patients' altruistic reasons for
555 participation. Establishing and maintaining a longitudinal relationship between participant and
556 interviewer can reduce loss to follow-up. As with other longitudinal studies, collecting contact
557 information of family members or friends in case the patient cannot be reached can aid in
558 retention. Recruitment and retention of pregnant women may be aided by a flexible follow-up
559 schedule (e.g., conducting follow-up interviews by telephone, during evening and weekend hours
560 or over a secure online platform), because participants may be balancing work and childcare
561 responsibilities.

14. Multiproduct Pregnancy Registries

562
563 To prevent overburdening patients, physicians, and health delivery systems with multiple
564 requests to participate in individual studies, we encourage sponsors to work together directly or
565 through consortiums to develop or support multiproduct registries. A multiproduct pregnancy
566 registry actively collects information on exposure to various product therapies in specific
567 diseases, such as human immunodeficiency virus or epilepsy (Hernández-Díaz et al. 2012). In
568 some cases, a general multiproduct registry, such as that conducted by a teratogen information
569 service, collects information on products for unrelated indications.¹⁶ Multiproduct registries
570 have advantages over single-product registries with respect to efficiency and economy. They
571 also have the advantage of having comparison groups of pregnant women unexposed to the drug
572 or biological product of interest readily available (see section IV.B.6., Comparator Selection —
573 Reference Group(s)).

15. Pregnancy Registry Discontinuation

574
575 We recommend that a pregnancy registry be continued until one or more of the following occurs:

- 576 • Sufficient information has accumulated to meet the scientific objectives of the registry
- 577 • The feasibility of collecting sufficient information diminishes to unacceptable levels
- 578 because of low exposure rates, poor enrollment, or loss to follow-up
- 579 • Other methods of gathering appropriate information become achievable or are deemed
- 580 preferable

16. Lactation Study Added on to a Pregnancy Registry

581
582 There is also often a need to collect lactation data to provide information on the safety of drugs
583 and biological products during breast-feeding. Pregnancy registries can be used to recruit and
584 enroll breast-feeding women in lactation studies. Some women enrolled in a pregnancy registry
585 are already taking a drug or biological product during pregnancy, and because they may be likely
586 to continue treatment after delivery, these women are an ideal population in which to study

¹⁶ See the MotherToBaby pregnancy studies conducted by the Organization of Teratology Information Specialists available at <https://mothertobaby.org/pregnancy-studies/>.

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596 product levels in milk. For information on how to conduct a lactation study, see the draft
597 guidance for industry *Clinical Lactation Studies: Considerations for Study Design*.¹⁷

598
599

V. COMPLEMENTARY STUDIES

601

602 Use of complementary studies with different study designs may help address the limitations
603 inherent to a pregnancy registry. Additionally, as more postmarketing safety information
604 becomes available from interim registry reports, spontaneous reports, or case series, a more
605 specific safety signal may become apparent. Thus, additional studies that complement data
606 obtained from pregnancy registries and other sources, referred to as *complementary studies* in
607 this guidance, can be implemented as the need arises to better understand the specific effects of
608 using a drug or biological product during pregnancy, and to more precisely quantify the
609 magnitude of an association between a pregnancy exposure and a specific outcome.

610

611 Complementary studies can be retrospective in design, using secondary data (i.e., data collected
612 for purposes other than to assess the safety of one specific drug or biological product).¹⁸

613 Common retrospective data sources and study designs used for complementary studies for
614 purposes of pregnancy-related research can include the following:

615

- 616 • Electronic data sources (e.g., insurance claims and electronic health record databases)
- 617 • Population-based surveillance and national registries or registers
- 618 • Population-based case control studies

619

620 These data sources and designs are discussed in the following subsections.¹⁹

621

A. Electronic Data Sources

622
623

624 Electronic data sources often contain a large number of records available for research. At the
625 time of publication of this guidance, electronic data sources readily available for pregnancy
626 research include electronic administrative claims databases and/or electronic health record
627 (EHR) databases, referred to collectively as *electronic health care data (EHD)* in this guidance.
628 Best practices for studies using these data sources have been described in guidance²⁰ and also
629 apply to pregnancy studies using EHDs.

630

¹⁷ 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>.

¹⁸ As the need arises, secondary data can be supplemented with additional data collection (e.g., maternal interview).

¹⁹ Methods used to identify and evaluate pregnancy outcomes in a pregnancy registry study described in section IV., Pregnancy Registries (e.g., study objective(s), outcome(s), comparators, exposure, confounders, statistical analysis plan) also apply when considering complementary studies and will not be repeated in this section. This section addresses concerns specific to the data sources selected for complementary studies.

²⁰ See the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013).

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631 Regardless of the specific type of electronic data sources and study design used, investigators
632 should fully understand and describe the strengths and limitations of the data source proposed
633 (including the population(s) covered, data elements captured and their validity, system(s) of care,
634 and system-specific clinical and pharmacy data) to evaluate whether the data source is
635 appropriate to address specific pregnancy-related hypotheses.
636

637 Pregnancy and/or live birth data from EHD sources have been developed and used in a variety of
638 ways to evaluate product exposure and/or safety during pregnancy (Devine et al. 2010; Andrade
639 et al. 2012; Taylor et al. 2015; Huybrechts et al. 2014). Despite its successful and growing use,
640 selection of an EHD source to evaluate drug or biological product safety in pregnancy should
641 reflect consideration of methods used to identify pregnancies, estimates of conception and
642 gestational age, linkage to offspring records, and ascertainment and validation of pregnancy and
643 birth outcomes. Each of these considerations is discussed below.
644

1. Methods to Identify Pregnancies

645
646
647 The ability to identify clinically recognized pregnancies and births using EHD is central to use of
648 any database capable of assessing product safety during pregnancy. Identifying live births in an
649 EHD is relatively straightforward because delivery codes are available and relatively reliable.
650

651 Sponsors should consider the implications of limiting a study population to that of only live
652 births, because birth defects likely to result in non-live birth outcomes would not be captured.
653 Failure to include non-live births in a study population primarily affects study generalizability;
654 however, it also may result in a biased relative risk estimate if the rate of pregnancy loss or
655 termination caused by the defect is higher in one group than the other.
656

657 Use of EHD to identify non-live birth pregnancy outcomes for assessment of safety signals is
658 challenging. Non-live birth outcomes may be identified in EHD by the presence of diagnostic
659 and/or procedure codes specific to the outcome. However, gestational age at the time of the
660 outcome may be difficult to estimate if gestational age-specific codes accompanying the outcome
661 codes are unavailable or unreliable. Without a reasonable estimate of gestational age, a reliable
662 assessment of pregnancy exposure is difficult unless the investigator has access to ultrasound or
663 laboratory data.
664

2. Estimates of Conception and Gestational Age

665
666
667 A valid estimate of gestational age, from which a conception date may be estimated, is critical
668 for determining the timing of an exposure during pregnancy. For studies assessing pregnancy
669 outcomes among live births only, several methods exist for identifying gestational age. These
670 include:
671

- 672 • U.S. birth certificates (when available)
- 673 • Diagnostic ICD codes found in EHD databases²¹ and algorithms using these codes
- 674 • EHR or ultrasound report

²¹ Given the potential variability in code validity by data source and outcome type (e.g., live birth versus stillbirth), codes to identify gestational age should be validated in each database.

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3. *Linkages to Offspring*

Common methods for mother-infant linkages in the United States include linkages using birth certificates and linkages using unique data elements within the same EHD source (Andrade et al. 2012). Linkages of pregnancies identified in EHD to offspring using birth or fetal death certificates or other sources (e.g., medical records, national or state birth defect surveillance registries) can provide the investigator access to several important variables that are not captured, poorly captured, or captured with inadequate detail in EHD sources (e.g., maternal/paternal race/ethnicity, maternal smoking status, parity, birth defects, some drug exposure, and precise estimates of gestational age and birthweight of the newborn).

Even when only EHD sources are available, study data can be enhanced by linking those from the mother to the offspring. Many EHD sources contain unique identifiers assigned to both the mother and infant that may reflect the relationship to the primary health insurance policyholder. Matching this number, as well as the mother's delivery date, to the newborn's date of birth often successfully links the mother's pregnancy to the infant's health records. However, if the newborn is covered under a different insurance policy than the mother, the linkage may be impossible or at least limited to the clinical information available on the birth certificate or other data sources.

In the United States, linkages of non-live birth outcomes identified in EHD sources to other data sources are limited. Some states require reporting of fetal deaths (after 20 weeks), and this information may be available to investigators on a case-by-case basis via the state's vital records department. Information collected by the state is often similar to that collected on a birth certificate, but specific data elements vary by state.

4. *Study Outcome Ascertainment and Validation*

Diagnostic and procedure codes contained in EHD sources can be used to identify and study product-associated MCMs. However, the presence of any single diagnostic code does not necessarily imply a correct diagnosis. Diagnostic codes may reflect coding errors, rule-out diagnoses, actual diagnoses, or the presence of an abnormality that has not yet been validated or characterized. The validity of diagnostic codes for specific birth defects varies greatly by specific defect and data source (Cooper et al. 2008; Palmsten et al. 2014). Outcome validation is still needed for all outcomes unless a high-performing algorithm has been previously validated for the specific outcome in the same (or similar) database under consideration. Some outcomes can be ascertained in multiple ways. For instance, preterm birth and "small for gestational age" may be identified through the presence of diagnostic codes or may be calculated using gestational age and birth weight data found on the birth certificate and/or medical record. Investigators should validate these outcomes in the specific database of interest if considering their use as endpoints in EHD studies.

For all birth outcomes identified using EHD, sponsors should use a *gold standard* method of validation such as a medical chart for the development of a testable algorithm. For MCMs, sponsors should use reviews by clinical experts (geneticists or dysmorphologists) and/or linkage

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721 to birth defect registries and/or birth certificate data. The use of only EHD without access to
722 such gold standard sources or, at a minimum, a high-performing validated algorithm measuring
723 the same outcome in the specific database being considered may result in inaccuracy.
724

B. Population-Based Surveillance and National Registries or Registers²²

725
726
727 Population-based birth defect data sources are part of surveillance networks that extend to an
728 entire group of people having similar demographics (e.g., the entire nation in some European
729 countries), or to similar groups of people (e.g., state or regional births in the United States). The
730 advantage of using birth defect surveillance registries for MCM identification or validation is
731 that the identified MCM cases have already been adjudicated. Many of these registries capture
732 and adjudicate birth defect information for live births, stillbirths/fetal deaths, and elective
733 terminations. Some international birth defect registries follow guidelines developed by the
734 World Health Organization, in collaboration with the CDC and the International Clearinghouse
735 for Birth Defects Surveillance and Research (ICBDSR). Birth defect definitions in these
736 registries include MCMs associated with chromosomal abnormalities, which may not be
737 applicable to outcomes associated with drug or biological product exposures.
738

739 If maternal exposure information is collected, much of it is obtained from obstetrical records. If
740 sponsors consider population-based birth defect registries for exposure-based complementary
741 studies, they may need to supplement the registries with drug or biological product exposure
742 information from targeted maternal interviews and/or link to prescription information when
743 personal interviews are not possible.²³
744

745 Population-based birth defect registries have the substantial advantage of having large sample
746 sizes that allow the study of relatively rare MCMs.
747

748 Examples of population-based birth defect surveillance networks include:
749

- 750 • State-based Surveillance (United States)
- 751
- 752 • Vaccine and Medications in Pregnancy Surveillance System (VAMPSS) (United
753 States)²⁴
- 754
- 755 • The ICBDSR²⁵
- 756

²² For the purposes of this section, the term *registry* is used interchangeably with *register* (a term more commonly used in Europe).

²³ International population-based birth defect registries, usually European, can link to other databases to obtain drug or biological product exposure and outcome information.

²⁴ <http://www.bu.edu/slone/research/studies/vampss/>

²⁵ <http://www.icbdsr.org/resources/annual-report/>

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- 757 • The European Registration of Congenital Anomalies and Twins, registries²⁶
758

759 Those that capture MCMs as a result of mandatory reporting allow for an accurate estimate of
760 incident birth defects in the network, especially when the numerator can be easily linked to the
761 number of pregnant women in the country or the region as the denominator during the study
762 period.
763

764 Regardless of the type of surveillance or registry selected for analysis, limiting observation only
765 to MCMs increases the risk of missing important toxic product effects that may be incompatible
766 with life or that may occur at different times during the pregnancy. Some registries, however, do
767 include stillbirths and elective terminations. Therefore, it is important to thoroughly understand
768 and describe what information is and is not available in the population-based registries
769 considered for a study, including what information is available on maternal drug or biological
770 product exposures.
771

C. Population-Based Case Control Studies

772

773
774 Case-control study designs (including nested designs) are frequently considered when there is a
775 need to collect additional information from the mothers through personal interviews, to obtain
776 additional information on infants, to request permission to review medical records, or to perform
777 long-term follow-up of the offspring. Case-control studies also may be needed if the registry is
778 unable to collect sufficient data to assess a safety signal previously identified from another data
779 source.
780

1. Selection of Pregnancy-Related Cases and Controls

781

782
783 Cases with pregnancy or infant outcomes of interest can be identified from EHD, or regional,
784 national, or international birth defect registries. The same concerns identified earlier in this
785 guidance for selection of controls or comparators for pregnancy registry studies (internal or
786 external controls) also apply to selection of controls or comparators for complementary case-
787 control studies (see section IV.B.6., Comparator Selection — Reference Group(s)). For any
788 study, it is most important to ensure that comparators or controls are selected from the same
789 disease population (internal controls) when possible. Controls can be identified from the same
790 EHD or vital statistics departments or from general (state, regional, or national) birth records
791 giving rise to the cases; alternatively, birth outcomes (cases and controls) can be identified from
792 exposure- or disease-based registries.
793

794 When a case-control design is considered to evaluate a pregnancy outcome, regardless of the
795 source from which cases and controls were identified, sponsors should validate case or control
796 status using medical records or other reliable sources such as birth defect registries or review by
797 clinical experts. Documentation of validation should be provided when selecting cases from
798 these data sources. Case status identified from national or international networks are usually
799 already validated.
800

²⁶ <http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/malformationcodingguides>

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801 2. *Exposure Assessment*

802
803 The advantages of obtaining additional information by interviewing the mother as part of a case-
804 control study include the ability to collect data on all types of drug or biological product
805 exposures, including those not covered by insurance (e.g., over-the-counter, supplements). An
806 additional strength is the ability to extend or adapt the interview to capture information not
807 available from other databases: personal or family history; race and other demographics; dose,
808 timing, and duration of product use; history of maternal disease or indication for medication;
809 comorbidities; and potential confounders such as body mass index, tobacco and alcohol use,
810 reproductive history, occupation (maternal and paternal), and the occurrence of breast-feeding.
811 At the interview, investigators can obtain informed consent to review medical records to confirm
812 diagnoses or to identify brand or lot, among others. If relevant, investigators can request
813 biological specimens (e.g., breast milk samples, buccal swabs for DNA testing) to test for
814 product penetrance or assess hereditary effects. Direct access to the mothers allows specialized
815 physical examinations and developmental follow-up of the offspring.

816
817 Exposure recall bias is always a concern for information obtained from maternal interviews,
818 because such self-reported data are collected after the pregnancy outcome (i.e., case status) is
819 known. Recall bias could be introduced if the accuracy of reported exposure is different between
820 cases and controls, for example mothers of birth defect cases may more accurately recall
821 exposures during pregnancy versus mothers of unaffected infants. Attempts to minimize this
822 bias could include selecting as controls mothers with other adverse pregnancy outcomes (e.g.,
823 malformed infants with chromosomal defects or with malformations other than the one(s) of
824 interest) or other serious medical problems. Another approach to minimize recall bias is the use
825 of pharmacy records among cases and controls to confirm reported drug or biological product
826 exposures, when available, although pharmacy data only provide information on prescription
827 fills and not necessarily on quantity consumed and may not include over-the-counter products.

828 829 3. *Examples of Pregnancy Case-Control Studies in the United States*

830
831 Examples of case-control studies are listed below and can be used as a starting point for
832 designing a study. Note, however, that data from these studies, although population-based, are
833 only specific to the populations studied and may not be relevant to the study population under
834 consideration. If comparisons are to be made to these studies, every effort should be made to
835 understand and explain the similarities and differences and to identify resulting confounding and
836 biases.

- 837
- 838 • The National Birth Defects Prevention Study²⁷
 - 839
 - 840 • Birth Defects Study to Evaluate Pregnancy exposures²⁸
 - 841

²⁷ <http://nbdps.org/>

²⁸ <http://www.bdsteps.org/>

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- 842
- 843
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- 845
- Pregnancy Health Interview Study (Birth Defects Study), a multicenter case-control study based at the Slone Epidemiology Center at Boston University, a collaborator of the VAMPSS²⁹

²⁹ <http://www.bu.edu/slone/research/studies/phis/>

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965 Guidances¹

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968 Draft guidance for industry *Clinical Lactation Studies: Considerations for Study Design*²
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¹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² 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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Guidance for industry and FDA staff *Best Practices for Conducting and Reporting
Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*

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APPENDIX A:

LIST OF DATA COLLECTION ELEMENTS

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The following data elements should be included when designing a pregnancy registry.

General

- Patient identifier
- Name of reporter at initial contact with the registry
- Date of initial contact with the registry
- Dates of any follow-up contacts
- Telephone number and email address of reporter
- Additional contact names, telephone numbers, and email addresses (if reporter is the patient)

Maternal Information

- Source of information (e.g., obstetrician, pregnant woman)
- Birth date
- Race
- Occupation
- Height, weight, body mass index
- Maternal medical history (e.g., hypertension, diabetes, seizure disorder, autoimmune disease, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures)
- Obstetrical history:
 - Number of pregnancies and outcome of each (live birth, miscarriage, pregnancy termination (elective or therapeutic), ectopic pregnancy)
 - Previous maternal pregnancy complications
 - Previous fetal/neonatal abnormalities and type
- Current pregnancy:
 - Date of last menstrual period
 - Ultrasound results for gestational dating
 - Prenatal test results (including dates)
 - Pregnancy weight gain of mother
 - Obstetric complications (e.g., preeclampsia, premature delivery)
 - Complications during pregnancy (including any adverse product reactions) and dates
 - Number of fetuses
 - Disease course(s) during pregnancy and any complications
 - Drug or biological product exposures (prescription drugs, over-the-counter products, and dietary supplements):
 - Name
 - Dosage and route
 - Date of first use and duration
 - Indication
 - Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount

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- 1027 Family history (specify type, maternal or paternal, among others):
1028 Malformations
1029 Genetic disorders
1030 Multiple fetuses/births
1031
1032 **Neonatal Information**
1033
1034 Initial:
1035 Source of information (e.g., obstetrician, pediatrician, mother)
1036 Date of receipt of information
1037 Date of birth or termination
1038 Gestational age at birth or termination
1039 Gestational outcome (live born, fetal death/stillborn, miscarriage, elective termination, and
1040 termination for a fetal anomaly)
1041 Sex
1042 Obstetric complications (e.g., preeclampsia, premature delivery)
1043 Pregnancy order (singleton, twin, triplet)
1044 Results of neonatal physical examination including
1045 Anomalies diagnosed at birth or termination (including autopsy results)
1046 Anomalies diagnosed after birth
1047 Weight at birth indicating whether small, appropriate, or large for gestational age
1048 Length at birth
1049 Head circumference at birth indicating whether small, appropriate, or large for gestational
1050 age
1051 Condition at birth (including, when available, Apgar scores at 1 and 5 minutes, umbilical
1052 cord vessels and gases, need for resuscitation, admission to intensive care nursery)
1053 Neonatal illnesses, hospitalizations, drug therapies
1054
1055 Follow-up:
1056 Source of information (e.g., pediatrician, mother)
1057 Date of receipt of information
1058 Anomalies diagnosed since initial report
1059 Developmental assessment
1060 Infant illnesses, hospitalizations, drug therapies
1061