Postapproval Pregnancy Safety Studies

Guidance for Industry

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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Postapproval Pregnancy Safety Studies Guidance for Industry[1]

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide sponsors[2] and investigators with recommendations on how to design investigations to assess the safety outcomes of pregnancies in women who are exposed to FDA regulated drug and biological products[3] during pregnancy (i.e., pregnancy safety studies) in the postmarketing setting. 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 by including the information in the *Pregnancy* subsection and other relevant sections of labeling. Clinical information needed to support a specific indication or comparative claims in pregnant women is outside the scope of this guidance.

Observational data may signal concern between the use of a drug during pregnancy and teratogenicity. Case reports may be used to describe rare outcomes during pregnancy that appear to be linked to a specific drug. Emerging methodologies could be considered to supplement data collected to assess the safety of drugs used during pregnancy.

This guidance should be used in conjunction with best practices guidelines for the design, conduct, and interpretation of observational studies using real-world data and with other relevant

[1] This guidance has been prepared by the Office of New Drugs, the Office of Surveillance and Epidemiology, and the Office of Translational Sciences 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. See 21 CFR 312.3(b).

[3] For the purposes of this guidance, the terms *drug(s), drug products*, and *drug and biological products* are used to refer to human prescription drug products regulated under section 505 of the FD&C Act (21 U.S.C. 355) and biological products regulated under section 351 of the Public Health Service Act (42 U.S.C. 262), other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

FDA guidance documents.[4] 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. Clinical information, such as randomized clinical trials, needed to support a specific indication or comparative claims in pregnant women is outside the scope of this guidance.

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

II. BACKGROUND

Pregnant women represent an important segment of the population, with approximately 3.6 million births occurring per year, based on national vital statistics in the United States (per 2025 data). Pregnant women may have chronic conditions such as diabetes, seizure disorders, or asthma, that need to be treated during pregnancy or may develop acute or other serious medical conditions during pregnancy that require treatment. Additionally, pregnant women may be advised to receive certain vaccines during the course of their pregnancies. Public health emergencies, such as a pandemic, highlight the need for safety data collection in pregnant women for new therapeutics and vaccines that are being developed on an urgent basis. In addition, 41.6 percent of pregnancies in the United States in 2019 were unintended,[5] which could result in potential inadvertent exposure to drugs in pregnancy if a woman takes a drug when she is not aware she is pregnant (Rossen et al. 2023). Therefore, there is an important need for safety information on product exposure during pregnancy.

Pregnant patients were historically excluded from clinical studies to protect fetuses from potentially harmful exposures. However, this exclusion results in a shift of risk to the postmarketing setting where there may be widespread use. Ideally, safety information on drugs used during pregnancy should be obtained in the premarketing setting with evidence from well-designed randomized clinical trials, as appropriate. However, during clinical development of most drugs and vaccines, pregnant women are actively excluded from trials, and if pregnancy does occur during a trial, the usual practice is to discontinue treatment and monitor pregnancy outcomes. Consequently, at the time of a drug's initial marketing, except for drugs developed to

[4] See the guidances for industry *Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products* (August 2023) and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) and the draft guidance for industry *Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products* (March 2024). When final, this guidance will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] An unintended pregnancy is a pregnancy that is unwanted (occurred when no children or no more children were desired) or mistimed (occurred earlier than desired)." Source: https://www.cdc.gov/reproductive-health/hcp/unintended-pregnancy/index.html.

treat pregnancy-specific conditions, there are typically no or limited human data to inform the safety of a drug taken during pregnancy. For this reason, postmarketing safety data collection is critical to identifying potential adverse effects to the developing fetus or mother.

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(3)), authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs approved under section 505(b) of the FD&C Act and biological products approved under section 351 of the Public Health Service Act (42 U.S.C. 262). FDA can require such studies or trials at the time of approval, on the basis of scientific data deemed appropriate by the Secretary,[6] to assess a known serious risk related to the use of the drug, to assess a signal of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk.[7] Under section 505(o)(3)(C), FDA can also require such studies or trials after approval if FDA becomes aware of *new safety information*.[8,9] Under section 505(o)(3), and specific to a pregnancy safety assessment, postapproval safety studies using data collected during pregnancy may be required, on the basis of scientific data deemed appropriate by the Secretary, for any of the purposes described in section 505(o)(3)(B) with respect to a serious risk to the pregnancy that may affect the health of the fetus or the pregnant woman caused by drugs used during pregnancy.[10] Specifically, the following are three periods of time during which follow-up data collection may be needed, depending on a drug's half-life and potential impact (Huybrechts et al. 2025):

1. Drug exposure prior to pregnancy: There may be a difference in the overall rate of pregnancy, ectopic pregnancy, implantation, or early pregnancy loss.

2. Data about drug exposure during pregnancy: The course of a disease during pregnancy may be different than the non-pregnant state (e.g., there may be a change in the rate of hypertension, preeclampsia, or hospitalization).

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[6] See section 505(o)(3)(A) of the FD&C Act.

[7] See section 505(o)(3)(B) of the FD&C Act.

[8] Defined at section 505-1(b)(3) of the FD&C Act. Also see the draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). 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/regulatory-information/search-fda-guidance-documents.

[9] Before requiring a postmarketing study or clinical trial under section 505(o)(3), FDA must find that the reports under section 505(k)(1) of the FD&C Act and the analysis system under section 505(k)(3) of the FD&C Act (active risk identification and analysis) will not be sufficient to meet the aforementioned purposes. Further, before requiring a postmarketing clinical trial, FDA must find that a postmarketing study or studies will not be sufficient to meet those purposes.

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

3. Postpartum monitoring: After delivery, medication use during pregnancy or the postpartum period may change the course of a patient's recovery (e.g., the rate of postpartum hemorrhage or postpartum diagnosis of hypertension) or the course of disease.

Often, observational studies such as pregnancy registries[11] and other pharmacoepidemiological studies can provide additional information, including a comparator group to derive and compare rates on safety outcomes of drugs used during pregnancy. Pregnancy registries are an important tool for safety data collection in the postmarketing setting because of the prospective study design and the ability to collect detailed patient-level data.[12] However, because of the recurring challenges of achieving sufficient enrollment, pregnancy registries are often not sufficient by themselves to assess the safety of drugs used during pregnancy; therefore, other study designs and data sources capable of adequately assessing the occurrence of pregnancy outcomes are used. In addition, use of complementary designs and data sources may help address the limitations inherent to a specific study design and provide greater confidence in the conclusions.

This guidance describes three general approaches (case reports and case series, prospective primary data collection through pregnancy registries, and complementary data sources) that can be used in the postmarketing setting to evaluate the safety of drug products used during pregnancy. These approaches are not intended to imply a hierarchy of evidence from the different study methods. Rather, each approach may uniquely contribute to the overall safety assessment of a product used during pregnancy. Discussion of selecting the most appropriate type of pregnancy safety study is beyond the scope of this guidance. Any available human safety data during pregnancy may be used to inform drug labeling, including the "Highlights of Prescribing Information" section. This guidance aims to discuss the strengths and limitations of each approach and further provide recommendations on how to plan and conduct each type of pregnancy safety study.

III. CASE REPORTS AND CASE SERIES

One source of pharmacovigilance data for safety signals is spontaneous adverse event reports submitted to the sponsor and FDA, as well as case reports from the peer-reviewed published medical literature or clinical studies. Well-documented and informative case reports can be used to identify a signal, particularly if the outcome in pregnancy is rare in the absence of drug exposure. Safety signals generally indicate that further investigation is warranted, which may or may not lead to the conclusion that the product caused the outcome or increased the risk of the outcome. Good pharmacovigilance practice includes the collection of comprehensive data on adverse pregnancy outcomes to detect safety signals and develop a case series for risk assessment analysis. Clinicians play a crucial role in identifying teratogenic exposures through

[11] 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.

[12] Registries established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug may be required as part of a risk evaluation and mitigation strategy (REMS) under section 505-1(f)(3)(F). When part of a REMS, registries are elements to assure safe use of the drug or biological product. These types of registries are not described further in this guidance.

the detection of distinctive and unique patterns of congenital malformations associated with particular pregnancy exposures (Shepard 1994; Obican and Scialli 2011). High-quality information in case 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 through pregnancy outcome as part of routine pharmacovigilance.

Interpretation of case reports can be challenging when information is incomplete or there are additional risk factors for the adverse pregnancy outcome. Informative case reports include several important elements for conducting pharmacovigilance.[13] Critical factors in evaluating the effects of product exposure during pregnancy may include, but are not limited to, the following:[14]

- A detailed description of the adverse fetal, infant, and/or maternal outcomes
- A detailed description of the exposure including the specific medication, dose, frequency, route of administration, and duration
- The timing of the exposure in relation to gestational age
- The maternal age, medical, reproductive and obstetric history, and use of concomitant medications, supplements, and other substances
- Exposures to other known or suspected environmental teratogens, genotoxins or potentially toxic exposures at home or in the workplace
- Family medical history of genetic conditions
- Data on clinical evaluations including obstetric or perinatal workup/evaluation and genetic assessment, if available.
- If fatal outcomes occur where there is a concern of potential causal effect from the drug, autopsy results, if available, should be obtained and provided to FDA in a timely manner.

Spontaneous postmarketing reports may be useful, but have limitations such as underreporting, incomplete information, or lack of a denominator (number of exposed patients and timing of exposure). These limitations pose challenges for case analyses and determining whether a causal relationship exists between a product exposure and an adverse pregnancy outcome. However, data should be reported even if some of the above details are not available.

Sponsors should view evaluation of a safety signal arising from case reports as the start of an iterative process that may require ongoing pharmacovigilance and additional studies. In

[13] See the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.

[14] See appendix, List of Data Collection Elements.

addition, sponsors should take the expected background rates of adverse pregnancy outcomes into account when interpreting the data. On rare occasions, FDA has considered case reports and case series (in the absence of other human data) to be adequate data sources for establishing a causal association for adverse pregnancy events, such as with isotretinoin and teratogenicity (Centers for Disease Control and Prevention (CDC) 1984; Rosa 1983) or trastuzumab and oligohydramnios (Zagouri et al. 2013). Case reports have been most useful and informative in situations where the adverse pregnancy outcome rarely occurs as a background event, and the adverse outcome is well documented.

IV. PREGNANCY REGISTRIES

A. Overview

A pregnancy registry actively collects information on patients exposed to a drug during pregnancy and associated pregnancy and birth outcomes; these data can be used to conduct a prospective[15] observational study (pregnant women are enrolled before the pregnancy outcome). Pregnancy registries are a type of real-world data collection[16] and depend on the voluntary participation of pregnant women who have been exposed to a specific drug and unexposed pregnant women who have not been exposed to the drug of interest. Pregnancy registry data are prospectively collected by maternal interview and medical record documentation and may include results of the clinical examination of the newborn (see appendix). Because of the prospective design of pregnancy registries, they may support assessment of the drug's possible association with multiple maternal, obstetrical, fetal, and infant outcomes, including pregnancies that do not result in live births.

A pregnancy registry may be U.S.-based or international in its scope.

Pregnancy registries have the following strengths:

- Prospective enrollment facilitates accurate ascertainment of exposure status and timing of the exposure in relation to gestational age, dose, frequency, and duration of the exposure, as well as covariates,[17] before pregnancy outcome is known and may therefore reduce exposure misclassification, recall bias, and confounding.

- By enrolling pregnant women exposed to the drug product of interest, pregnancy registries can be an efficient way to collect data on the effects of rare exposures during pregnancy or delayed adverse effects.

[15] Ibid.

[16] See the guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023).

[17] See appendix, List of Data Collection Elements.

- Pregnancy registries capture outcomes in a broader population of pregnant women under real-world conditions.

- A pregnancy registry can be initiated and start to accrue real-time data as soon as a product becomes commercially available, in contrast to the use of medical claims data and electronic health records (EHRs) where there will be a lag time in data availability.

- A pregnancy registry can be designed to use structured data collection on a variety of pregnancy and infant outcomes, including postnatal outcomes.

- A pregnancy registry can be designed to include data from physical examination of the newborn and periodic clinical assessment of the offspring of exposed mothers, enabling access to detailed clinical information about outcomes of interest, without relying on administrative billing codes.

- Registries may be helpful in identifying a pattern of congenital abnormalities, preterm birth, or adverse pregnancy outcomes in exposed pregnancies or long-term developmental effects.

Pregnancy registries have the following limitations:

- Patient and provider recruitment, awareness, enrollment, and retention are often challenging.

- Incomplete outcome data due to dropouts or lack of long-term follow-up (e.g., missed miscarriages, postnatal outcomes).

- Difficulty in enrollment may lead to insufficient power to detect a statistically significant association. Small sample size may limit the study's ability to assess the drug's effect on pregnancy safety outcomes.

- Most pregnancy registries are designed primarily to assess the overall risk of major congenital malformations (MCMs).[18] Effects on less common, specific MCMs may be missed, however, because of small sample sizes for all but the most potent teratogens.

- Identification of an appropriate comparator group, though highly recommended, may not always be feasible in every case.

- Generalizability issues as findings may not apply to all populations (e.g., geographic variations).

[18] For the purposes of this guidance, the following terms are used interchangeably: *congenital malformations*, *congenital anomalies*, *birth defects*, and *MCMs*.

- Patients who choose to enroll in a registry may have different risk factors or demographics compared with other pregnant patients (selection bias). This could impact both internal and external validity of subsequent study findings.

B. Registry Design Considerations

Sponsors should submit study protocol(s) for FDA review before initiating a study. To assess whether a pregnancy registry will provide safety data that can inform product labeling, sponsors should conduct a feasibility study. Plans to assess feasibility should be included in the protocol, based on the assumptions on anticipated incidence of the outcomes, drug usage, and registry enrollment. Those assumptions should be periodically evaluated as data accumulate. The feasibility assessment may also include cumulative analyses of worldwide postmarketing safety data. A well-written protocol for a pregnancy registry should describe its objectives, study designs, and plans for structured data collection and analysis. The following issues should be addressed in the protocol to ensure consistency and standardization of data collection and analysis.[19]

1. Objectives

The protocol should state the objectives of the registry. The goal of the pregnancy registry is typically broad-based signal detection and includes comparative analyses for pregnancy, fetal, and infant safety outcomes. An effective pregnancy registry has the potential to serve as an early warning system to identify a new potent teratogen soon after market introduction. For less potent teratogens or for drugs that cause other adverse pregnancy outcomes, a pregnancy registry can function as a signal detection study and generate hypotheses that can be tested using other methods that may be better powered to assess specific adverse pregnancy outcomes, birth defects or other abnormalities.

2. Study Population for Inclusion

Ideally, pregnant women in the exposed and unexposed cohort should be enrolled in a pregnancy registry prospectively (i.e., before the conduct of any prenatal tests that could provide knowledge of the outcome of pregnancy). If the condition of the fetus has already been assessed through prenatal testing (e.g., targeted ultrasound, amniocentesis), such reports traditionally have been considered retrospective. However, because it may be difficult to obtain enrollment before prenatal testing on a consistent basis, the study population should include all pregnant women, including those who have had early prenatal testing. Subgroups of the study population may also be considered (e.g., by trimester of exposure, dose, or indication).

[19] See appendix, List of Data Collection Elements.

3. Outcome Definition(s) and Ascertainment

A pregnancy can result in live birth, miscarriage (loss before 20 weeks), pregnancy termination, or fetal death/stillbirth (loss at or after 20 weeks).[20] In the event of a non-live pregnancy outcome, when feasible, assessment of the fetus and, in certain circumstances, the placenta could be used to further evaluate the etiology for the adverse outcome. As part of the study design, the protocol should state a priori criteria for defining study outcomes. The protocol should clearly state criteria for defining birth defects as *major*. For example, MCMs might be defined as "abnormalities in structural development that are medically or cosmetically significant, are present at birth, and persist in postnatal life unless or until repaired." Similarly, criteria should be established for abnormalities that will be excluded from the definition of outcome (e.g., those that are minor, transient, chromosomal, genetic, positional, or prematurity-related) (Holmes and Westgate 2011). A standardized classification system should be used, as appropriate. To adjudicate outcomes, an expert clinical geneticist, dysmorphologist, or pathologist, as applicable, should review and classify medical records and reports of all MCMs. The clinical expert reviewer and method of assessment should be the same for both the exposed and the comparator group(s), and the reviewer should be blinded to the exposure status.

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

- Prenatal test results that may inform the reason for a non-live pregnancy outcome
- Measures of fetal growth deficiency (e.g., small for gestational age)
- Preterm delivery
- Other pregnancy-related complications such as gestational diabetes and pre-eclampsia
- Developmental milestones or neurologic abnormalities in offspring of exposed mothers
- Abnormalities of immune system development in offspring of exposed mothers
- Adverse events in the breastfed infant and potential effects of continued postnatal exposure through breastfeeding
- Outcomes specific to known safety issues of a product or class of drugs

[20] See Obstetric Care Consensus #10: Management of Stillbirth (March 2020) from the American College of Gynecology, available at https://www.acog.org/clinical/clinical-guidance/obstetric-care-consensus/articles/2020/03/management-of-stillbirth.

4. Alternative Study Design When an Adequately Powered Study Is Not Feasible

There are situations where very rare exposure to a drug during pregnancy is anticipated and a pregnancy registry or other type of observational study is unlikely to achieve adequate power to allow statistical inference. Examples include, but are not limited to, the following situations:

- Pregnancies exposed to treatment for rare diseases or conditions that occur rarely in females of reproductive potential.

- Where labeling recommends against use of the drug during pregnancy based on potential safety findings (e.g., concerning human data and/or animal reproductive toxicology studies).

- For drugs not likely to be used during pregnancy because of an unfavorable benefit-risk ratio.

In these situations, a descriptive pregnancy safety study may be an alternative study method to obtain follow-up information on exposed pregnancies. Sponsors should submit protocols including study designs, objectives, and plans for structured data collection and analysis.[21] Anticipated issues with study feasibility should be stated in the protocol and appropriately addressed, for example, by expanding the inclusion criteria to include all reports of exposed pregnancies (both prospective and retrospective). A predefined target sample size may not be feasible; however, sponsors should provide estimates of pregnancy exposure. This type of exposed pregnancy cohort can inform clinical and regulatory decision-making when exposures during pregnancy are rare.

Similar to pregnancy registries, sponsors should be encouraged to add a phone number and website address to product labeling to facilitate participation in the descriptive pregnancy safety study and health care provider reporting regarding exposed pregnancies.[22] Safety data collection from all countries where the product is marketed is usually needed to maximize the number of exposed pregnancies that are available for clinical safety assessment. Sponsors should consider additional patient and health care provider awareness activities for rare disease populations to encourage pregnant patients and health care providers to participate in the ongoing safety data collection (e.g., rare disease patient support groups) (see section IV.B.12., Recruitment and Retention Plans).

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

[22] See the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2020). When final, this guidance will represent the FDA's current thinking on this topic.

5. 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. When sponsors evaluate a specific drug used as one treatment in a multiproduct or disease-based registry study (e.g., autoimmune diseases), cohorts exposed to different treatment regimens within the registry can serve as additional internal comparator groups (see section IV.B.13., Multiproduct and Disease-Based Pregnancy Registries).

A background rate or the prevalence of congenital anomalies in a population-based surveillance system (e.g., Metropolitan Atlanta Congenital Defects Program (MACDP))[23] 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); the definition for outcomes of interest may differ from the registries (particularly with regard to chromosomal abnormalities); and the duration of postnatal follow-up. More 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 in pregnant women undergoing treatment for a given disease, such as diabetes or asthma. This is particularly true if there is evidence that prevalence of congenital abnormalities differs in the indicated patient population compared to the general population.

When available and feasible, sponsors can consider use of external databases with data on background rates of pregnancy outcomes 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.

6. Exposure Definition and Ascertainment

Sponsors should collect detailed information on start and stop dates for all drugs 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 drugs 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 because risks of adverse outcomes, including teratogenicity risk, may vary greatly by pregnancy trimester.

[23] See the CDC's MACDP web page at https://www.cdc.gov/ncbddd/birthdefects/macdp.html.

7. 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 drugs or the underlying disease. Data should be collected on the pregnant woman's pertinent medical history, current disease status, and overall management. Other potential confounders for which data should be collected include, for example, socioeconomic status, maternal age, pre-pregnancy maternal weight indices, tobacco and alcohol use, illegal drug use, folic acid and vitamin use, drug exposure before and during pregnancy, obstetrical history, medical history, family history of adverse pregnancy outcomes including MCMs (Richardson 2023).

8. Data Collection

The ability of the pregnancy registry to adequately address regulatory safety questions depends on the accuracy and comprehensiveness of its data. All data collection efforts should be identical among exposed and comparator study groups to minimize bias.

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

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

See appendix for a list of recommended data elements to include when designing a pregnancy registry.

9. Statistical Methods

The statistical methods for a pregnancy registry study should be prespecified in the protocol and the details provided in either the protocol or a separate statistical analysis plan document.

a. Sample size and statistical power

The protocol should include a target sample size. The target sample size should incorporate the background rate of pregnancy loss, if applicable, and cases that may be lost to follow-up or otherwise unevaluable. Estimated background rates should also consider known or potentially

associated adverse pregnancy outcomes of interest in the target population including the specific disease of interest.

To conduct comparative analyses, the sponsor should determine the sample size based on power calculations. An adequate sample size depends on the study objective(s), design of the registry, the clinically meaningful risk the study intends to detect or rule out, and the background rate of the outcome in the study population or comparator group. Sponsors should include justification for the choice of expected background rates for outcomes of interest and the choice of clinically meaningful risk in their proposed sample size and power calculations.

If more than one study outcome is considered, the sponsor should determine sample size based on the outcome with the lowest background rate (e.g., MCMs) in the primary objective.

Typically, a specific defect or pattern of defects is associated with a specific teratogenic exposure during a critical period. Some specific MCMs occur rarely in the general population (i.e., fewer than 1 in 1,000 live births). Historically, pregnancy registries have not had sufficient sample size or power to evaluate increased risks for specific MCMs unless the relative risks are large (Gelperin et al. 2017; Bird et al. 2018). Therefore, most registries compare the overall proportion of the total combined number of various MCMs observed in the exposed group to the overall proportion in a comparator group(s).

b. Data analysis and presentation

Descriptive statistics are the primary approach for summarizing patient characteristics and additional data from a pregnancy registry. Separate analyses should be performed for each pregnancy outcome (miscarriage, pregnancy termination, fetal death/stillbirth, live birth) and stratified by gestational timing of exposure (with a separate analysis of first trimester exposures) to capture the majority of MCMs or additional analyses depending on the outcome or the exposure window of interest.

For comparative analyses, the protocol should list covariates and factors that may affect the study findings, such as gestational age at the time of enrollment (Margulis et al. 2015) and whether informative prenatal testing has been done. These potential confounders, covariates that influence the outcome and the exposure status, should be adjusted using analysis methods. The specific discussion of the analysis methods is beyond the scope of this guidance. However, sponsors should include details of how they intend to adjust for confounders and methods to diagnose the corresponding assumptions in the protocol.

Given the heterogeneous nature of data obtained in pregnancy registries, there is no single format for data presentation that is applicable for all studies. The choice of a final format depends on outcomes identified in the registry protocol, unanticipated findings, and expert advice. We encourage sponsors to develop forms of data presentation and analysis that fully capture outcomes of concern within their particular registry. In studies that investigate the total combined number of various MCMs, sponsors should aim to describe and quantify imbalances in specific malformations or patterns of specific malformations that may drive imbalances in the total number of MCMs. Although a pregnancy registry may not be adequately powered to detect

a specific MCM, imbalances should be noted and considered for further evaluation as appropriate. Statistical significance is not a requirement for safety signal detection. Sponsors should report the proportion of participants with missing adverse pregnancy outcome and infant status data. Flowcharts are often used to illustrate these missing data. When submitting interim and final pregnancy registry study reports, sponsors may include cumulative analyses of worldwide postmarketing safety data, when available, to provide perspective on registry feasibility and updates on available safety data in pregnant women that may not be included in the registry.

10. Privacy and Human Subject Protection Issues

Sponsors should consider privacy (including data protection) and human subject protection (including obtaining informed consent and institutional review board (IRB) oversight) when designing a pregnancy registry and developing protocols for the subsequent use of the data from the registry. FDA recommends that an IRB be consulted when developing a pregnancy registry to ensure that the collection of data and all other procedures associated with the registry will be done in accordance with current ethical standards.

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

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

11. Independent Data Monitoring Committee/Scientific Advisory Board

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

12. Recruitment and Retention Plans

Successful recruitment and retention strategies are critical to the success of pregnancy studies such as registries or other studies requiring enrollment of study subjects. We recommend a robust recruitment and retention plan that includes a multipronged approach to ensure widespread coverage of the eligible population. Early enrollment may improve detection of miscarriages. These plans should be flexible and continuously reassessed throughout the study to ensure the registry maintains an adequate number of eligible pregnant women in both the exposure and comparator group(s).

a. Recruitment

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

Under the pregnancy and lactation labeling rule requirements, if there is a pregnancy registry for the product, relevant contact information must be included in product labeling under the subheading Pregnancy Exposure Registry.[24] Suggested modes of contact information include a toll-free telephone number or a website's uniform resource locator (URL).

Recruitment strategies can be health care provider initiated, facility based, or patient initiated.

- Health care provider-initiated recruitment of patients is an important deciding factor for many pregnant women. Provider recruitment approaches include the following:

  - Announcement of the registry study and contact information in the product labeling
  - Promotional materials and product Internet pages
  - Announcements in professional journals and newsletters
  - Personal mailings to specialists
  - Presentations and exhibits at professional meetings

- Facility-based recruitment can occur at the level of a practice or health system. Health care facilities may be able to use their EHRs to identify women prescribed the drug to facilitate the enrollment process for providers. For example, an automated alert of a pregnancy registry can be generated in response to positive pregnancy test results and/or specific drug prescriptions.

- Patient-initiated recruitment efforts when appropriate rely on patients to contact the registry study staff and self-enroll. Because pregnancy is often recognized by the patient first, registries that enroll patients directly can allow for recruitment of patients earlier in

[24] 21 CFR 201.57(c)(9)(i)(A).

pregnancy. Useful avenues to notify pregnant women of pregnancy registries include the following:

- Print media including publications, press releases, and articles in newspapers and magazines with pregnant women among their readerships

- Distribution of flyers and posters in locations such as hospitals, ultrasound clinics, laboratories, prenatal classes, community centers, stores, and coffee shops (Webster et al. 2012)

- Social media

- Downloadable applications for mobile devices or personal computers could enable broader participation through ease of providing information

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

- Incentives that facilitate study participation (Goldstein et al. 2021)
- Employing empathetic, culturally sensitive, and personable study staff

b. Retention

Even though recruitment materials may yield strong initial recruitment results, we recommend implementing a robust retention plan to ensure that an adequate number of pregnant women remain in the registry. The retention plan should address specifics of patient retention strategies, contingency plans to obtain follow-up information, methods to track follow-up rates over time (e.g., interim and final data reports), and implementation steps to improve follow-up if expected follow-up rates are not met.

FDA also recommends that retention efforts focus on participating health care providers to improve retention rates and reduce the burden of data collection (e.g., implementing streamlined processes and succinct forms). Access to pregnancy registry results provides a strong incentive for the participation of health care providers, particularly obstetric care providers, and the provision of interim data reports to participating health care providers may bolster retention. Additionally, high levels of retention have been achieved by pregnancy registries that communicate directly with patients. Emphasizing the mission of the pregnancy registry may reinforce participants' motivation to remain in the study. Sharing study results through a newsletter or website has been found to be effective in reinforcing patients' altruistic reasons for participation. Establishing and maintaining a longitudinal relationship between participant and interviewer can reduce loss to follow-up. As with other longitudinal studies, collecting contact information of family members or friends in case the patient cannot be reached can aid in retention. Recruitment and retention of pregnant women may be aided by a flexible follow-up schedule (e.g., conducting follow-up interviews by telephone, during evening and weekend hours, or over a secure online platform) because participants may be balancing work and/or childcare responsibilities.

13. Multiproduct and Disease-Based Pregnancy Registries

We encourage sponsors to work together directly or through consortia to develop or support multiproduct registries or disease-based registries. A multiproduct pregnancy registry actively collects information on exposure to various product therapies in specific diseases, such as human immunodeficiency virus or epilepsy (Hernández-Díaz et al. 2012). In some cases, a general multiproduct registry, such as that conducted by a teratogen information service, collects information on drugs for unrelated indications.[25] Disease-based registries may include patients who are not treated and those who receive treatment(s) of interest. Multiproduct registries and disease-based registries have advantages over single-product registries with respect to efficiency, economy, and public awareness. In certain instances, they can also provide readily available, internal comparison groups of pregnant women who are either unexposed or exposed to different drugs of interest (see section IV.B.5., Comparator Selection — Reference Group(s)).

14. Pregnancy Registry Discontinuation

The longer a pregnancy registry continues, the greater the likelihood of developing meaningful data on potential adverse pregnancy outcomes, and in particular, the frequency of malformations. However, a pregnancy registry may be discontinued when one or more of the following occurs:

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

15. Postpartum Maternal Monitoring and Lactation Study

Postpartum maternal events should be monitored to assess the impact of medication on outcomes such as postpartum hemorrhage, hypertension, and the disease course.

Lactation data (possibly as a follow-up study) are often collected to provide information on the safety of drugs to infants fed breast milk. Pregnancy registries can be used to recruit and enroll lactating women in lactation studies. Some pregnant women enrolled in a pregnancy registry are already taking a drug during pregnancy, and because they may be likely to continue treatment after delivery, are an ideal population in which to study product levels in breast milk. For information on how to conduct a lactation study, see the draft guidance for industry *Clinical Lactation Studies: Considerations for Study Design* (May 2019).[26]

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[25] See the MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists available at https://mothertobaby.org/pregnancy-studies/.

[26] When final, this guidance will represent the FDA's current thinking on this topic.

V. COMPLEMENTARY STUDIES

Use of complementary studies with different study designs or data sources may help address the limitations inherent to a pregnancy registry (e.g., limited statistical power, selection bias). Additionally, as more postmarketing safety information becomes available from interim registry reports, spontaneous reports, or case series, a more specific safety signal may become apparent. Additional observational studies that complement data obtained from pregnancy registries (referred to as *complementary studies* in this guidance) should be implemented, when appropriate, to better understand the specific effects of using a drug during pregnancy and to quantify more precisely the magnitude of an association between a pregnancy exposure and a specific outcome. In selecting data sources, sponsors should also be cognizant of the potential for capturing the same pregnancy in two different data sources (*double counting*).

Complementary studies typically use secondary data (i.e., data collected for purposes other than to assess the safety of one specific drug).[27] Common study designs for complementary studies for purposes of pregnancy-related research are cohort studies, or case-controls studies that use the following retrospective data sources:

- Electronic data sources (e.g., medical claims data and EHR data)
- Population-based surveillance and national registries or registers

These data sources and designs are discussed in the following subsections.[28] Integration of multiple data sources is useful to characterize the safety of medication use during pregnancy.

A. Cohort Studies Using Electronic Data Sources

Electronic data sources often contain a large number of records available for research. At the time of publication of this guidance, electronic data sources readily available for pregnancy research include electronic administrative claims databases and/or EHR databases, referred to collectively as *electronic health care data (EHD)* in this guidance. Best practices for studies using these data sources have been described in guidances[29] and also apply to pregnancy studies using EHD.

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[27] Where beneficial, secondary data can be supplemented with additional data collection (e.g., maternal interview).

[28] 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.

[29] See the ICH guidance for industry *M14 General Principles on Planning, Designing, Analyzing, and Reporting of Non-interventional Studies That Utilize Real-World Data for Safety Assessment of Medicines* (March 2026). See also the guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (July 2024).

Regardless of the specific type of electronic data sources and study design used, investigators should fully understand and describe the strengths and limitations of the data source proposed (including the population(s) covered, data elements captured and their validity, system(s) of care, system-specific clinical and pharmacy data, and expected number of pregnant women exposed to the drug) to evaluate whether the data source is appropriate to address specific pregnancy-related question(s). The adequacy of data sources and feasibility assessment results should be discussed in the protocol.

Pregnancy and/or live birth data from EHD sources have been developed and used in a variety of ways to evaluate product exposure and/or safety during pregnancy (Huybrechts et al. 2019). Selection of an EHD source to evaluate drug safety in pregnancy should reflect consideration of methods used by the EHD source to identify pregnancies, methods used for estimates of gestational age and the start of pregnancy, mother-infant linkage, ascertainment and validation of pregnancy, birth, and infant outcomes including gestational age at delivery, exposure ascertainment, and confounder adjustment. Each of these considerations is discussed below.

1. Methods to Identify Pregnancies

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

Sponsors should consider the implications of limiting a study population to that of only live births because birth defects likely to result in non-live birth outcomes would not be captured, resulting in live-birth bias. Failure to include non-live births in a study population primarily affects study generalizability; however, it also may result in biased effect estimates if the rate of pregnancy loss or termination caused by the defect is higher in one group than the other. Investigators should perform secondary or exploratory analyses to examine outcomes among non-live births. Investigators should also perform bias analysis to account for factors that may impact risk estimates.

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

2. Estimates of Start of Pregnancy and Gestational Age

A valid estimate of gestational age, from which a pregnancy start date (i.e., date of last menstrual period plus 14 days) may be estimated, is critical for determining the timing of an exposure during pregnancy. Several methods exist for identifying gestational age. Details of the source of

information and the method(s) used should be clearly described in the protocol along with any validation data. Methods can include the following:

- Fetal death certificates for non-live birth outcomes (when available)
- Diagnostic ICD codes found in EHD databases[30] and algorithms using these codes
- EHR or ultrasound report
- Timings when reproductive technology is utilized (e.g., in vitro fertilization)

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 certificates, 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, precise estimates of gestational age and birth weight of the newborn).

To obtain infant outcomes associated with exposure during pregnancy in EHD sources, study data from mothers must be linked 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, for claims data if the newborn is covered under a different insurance policy than the mother, the linkage may be challenging as available data may be limited to the clinical information available on the birth certificate or other data sources. The quality of mother-infant linkages will depend on the availability and completeness of the data, and specifically the variables described above, which are used to provide linkage. Mother-infant linkage success should be described in the protocol and evaluated carefully to avoid potential selection bias.

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

Investigators can use diagnostic and procedure codes contained in EHD sources to identify and evaluate association of product and MCMs or other neonatal or maternal outcomes. 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

[30] 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, unless a high-performing algorithm has been previously validated for the specific outcome in the same (or similar) database under consideration.

of an abnormality that has not yet been validated or characterized. The validity of diagnostic codes for specific birth defects may vary widely by specific defect and data source (Chomistek et al. 2023; Palmsten et al. 2014). Some outcomes can be ascertained in multiple ways (Zhu et al. 2023; Moll et al. 2021; Andrade et al. 2021). 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. For all study outcomes identified via EHD sources, diagnostic codes or algorithms should be described in the protocol with sufficient detail to be reproducible.

For prespecified outcomes, FDA considers validation of algorithms used to identify study outcomes in the same (or similar) database to be the best practice unless a well-validated algorithm that is fit for purpose has been identified. Investigators should use a *gold standard* method of validation such as a medical chart review for the development of a testable algorithm. To evaluate a previously identified safety signal, sponsors should consider validating case status using medical records or other reliable sources such as birth defect registries or review by clinical experts. For birth outcomes such as MCM, board-certified geneticists or dysmorphologists should perform chart reviews. The use of only medical claims data without access to such gold standard sources may result in misclassification.

Outcome data can also be obtained through linkage to birth defect registries, birth certificate data, and other relevant sources of information. For more information, see discussion of data linkages in EHD described in previous guidances.[31]

Investigators should carefully consider the type of EHD because it may inform the completeness of outcome data. For example, closed administrative health care insurance claims data include all procedures, visits, and medications billed to a participant's health insurance. For outcome ascertainment in pregnancy studies, medical claims data may be preferred to EHR data because claims capture outcomes across multiple health care settings. However, linkage of claims to detailed EHR data may provide opportunities for outcome validation.

5. Exposure Ascertainment

Where available, pharmacy codes with dispensing information can be used to identify exposures to drugs. For some medications, procedure codes may also be used. For some EHD sources such as EHRs where pharmacy data may not be available, prescribing information from the EHR can be used. Investigators should carefully define exposure windows with consideration for drugs with long half-lives taken before the start of pregnancy and through the end of pregnancy. Investigators should also calculate trimester-specific exposure because often the first trimester is of concern for congenital malformations. For different drugs and study outcomes, there may be critical time periods of concern, and investigators can perform additional analyses by each trimester of exposure.

With EHD, exposure misclassification may occur when only prescribing or dispensing information is available, not actual use. A patient may stop taking a medication upon a positive

[31] See ICH M14. See also the guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products*.

pregnancy test or while planning to be pregnant; thus, dispensing information does not indicate that the medication was actually used in totality or at all. Investigators should use different sensitivity analyses (e.g., greater than or equal to two dispensings during pregnancy) and bias analyses to evaluate the robustness of study findings. For medications that are taken as needed (e.g., acute medication for pain), the dose, frequency, and exact timing of use would not be captured. Investigators should consider additional methods to address this limitation (e.g., patient surveys for exposure validation, patient diary).

6. Measurement of Covariates/Potential Confounders

Because observational studies are not designed as randomized trials, confounding can occur. Investigators should identify a priori all potential confounders that may impact the exposure-outcome association. Information on potential confounders can be used to balance the treatment and comparator arms in the analysis. For a pregnancy study, covariates may include maternal age, race/ethnicity, pre-pregnancy body mass index, personal or family history of pregnancy complications, behaviors (e.g., smoking during pregnancy, alcohol use during pregnancy, illicit drug use during pregnancy), indication for study drug usage, concomitant medications, and comorbidities. Investigators should measure for potential confounders in a predefined pre-pregnancy window that is long enough to reasonably capture claims or visits.

Investigators should also consider identification of potential time-varying covariates that occur during pregnancy. These may include, but are not limited to, pregnancy complications, concomitant medications, lifestyle factors, and comorbidities. For these time-varying covariates, timing relevant to exposure and study outcomes is critical. Ideally, these time-varying covariates should be assessed at a minimum during each trimester of pregnancy; however, it may be difficult to assess exact timing in certain data sources (e.g., administrative claims databases).

When relevant, algorithms used to capture potential confounders should be well validated.

More information on best practices for sample size considerations, covariate ascertainment, adjustment, and validation in EHD have been described in previous guidances.[32]

B. Population-Based Surveillance and National Registries or Registers[33]

Population-based birth defect data sources are part of surveillance networks that extend to an entire group of individuals having similar demographics (e.g., the entire nation in some European countries) or to similar groups of individuals (e.g., state or regional births in the United States). One advantage of using birth defect surveillance registries for MCM identification or validation is that the identified MCM cases have already been adjudicated. Many of these registries capture and adjudicate MCM information for live births, fetal deaths/stillbirths, and pregnancy

[32] See ICH M14. See also the guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products*.

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

terminations. Some international birth defect registries follow guidelines developed by the World Health Organization, in collaboration with the CDC and the International Clearinghouse for Birth Defects Surveillance and Research. Birth defect definitions in these registries include MCMs associated with chromosomal abnormalities, which may not be applicable to outcomes associated with drug exposures.

If maternal exposure information is collected, much of it is obtained from obstetrical records. If sponsors consider use of population-based birth defect registries for exposure-based complementary studies, they should supplement the registries with drug exposure information from targeted maternal interviews and/or link to prescription information when personal interviews are not possible.[34]

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

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

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

C. Case-Control Studies

Case-control studies (including population-based and nested designs) are frequently considered when collection of additional information from the mothers through personal interviews is warranted (e.g., to obtain additional information on infants, to request permission to review medical records, or to perform long-term follow-up of the offspring). Case-control studies also may be recommended if the registry is unable to collect sufficient data to assess a safety signal previously identified from another data source.

1. Selection of Pregnancy-Related Cases and Controls

Cases with pregnancy or infant outcomes of interest can be identified from EHD, or regional, national, or international birth defect registries. Some of the same concerns identified earlier in this guidance for selection of comparators for pregnancy registry studies (internal or external comparators) also apply to selection of controls or comparators for case-control studies (see section IV.B.5., Comparator Selection — Reference Group(s)). For any study, it is most

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

important to ensure that comparators or controls are selected from the same disease population (internal controls), when possible. Controls can be identified from the same EHD or vital statistics departments or from general (state, regional, or national) birth records giving rise to the cases; alternatively, birth outcomes (cases (infants with anomalies) and controls (infants without anomalies)) can be identified from exposure- or disease-based registries.

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

If an international network is used, a sponsor should discuss with the Agency how the study outcomes can be generalizable to the United States before initiating the study.

2. Exposure Assessment

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

Exposure recall bias is always a concern for information obtained from maternal interviews because such self-reported data are collected after the pregnancy outcome (i.e., case status) is known. Recall bias could be introduced if the accuracy of reported exposure is different between cases and controls; for example, mothers of infants born with birth defects may more accurately recall exposures during pregnancy versus mothers of unaffected infants. Attempts to minimize this bias could include selecting as controls mothers with other adverse pregnancy outcomes (e.g., infants with chromosomal defects or malformations other than the one(s) of interest) or other infants with other serious medical problems (such as complications that could be due to prematurity). Another approach to minimize recall bias is the use of pharmacy records among cases and controls to confirm reported drug exposures, when available. Note that pharmacy data only provide information on prescription dispensings and not necessarily on quantity consumed and may not include use of nonprescription drugs or supplements.

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Draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019)[4]

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Draft guidance for industry *Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products* (March 2024)

Guidance for industry *Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products* (August 2023)

Guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (July 2024)

Guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023)

Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005)

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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/regulatory-information/search-fda-guidance-documents.

[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/regulatory-information/search-fda-guidance-documents.

[3] When final, this guidance will represent the FDA's current thinking on this topic.

[4] When final, this guidance will represent the FDA's current thinking on this topic.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

ICH guidance for industry *M14 General Principles on Planning, Designing, Analyzing, and Reporting of Non-interventional Studies That Utilize Real-World Data for Safety Assessment of Medicines* (March 2026)

APPENDIX:
LIST OF DATA COLLECTION ELEMENTS

The following data elements should be included in a case report and 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 weight indices
- 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 (include reason for termination), ectopic pregnancy)
- Maternal pregnancy complications in previous pregnancies
- Fetal/neonatal abnormalities in previous pregnancies and type

Current pregnancy:
- Date of last menstrual period
- Ultrasound results for gestational dating
- Prenatal test results (including dates), including for pregnancies that do not result in live birth
- 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 exposures (prescription products, over-the-counter products, and dietary supplements):
  - Drug name
  - Dosage, frequency and route
  - Date of first use and duration, stop date
  - Prescribing indication

Concomitant exposures including vaccinations and environmental/occupational exposures
Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount
Family history (specify type, maternal or paternal, among others):
- Malformations
- Genetic disorders
- Multiple fetuses/births

Pregnancy Outcome Information

Initial
Source of information (e.g., obstetrician, pediatrician, mother)
Date of receipt of information
Date of birth or termination
Gestational age at birth or termination
Pregnancy outcome (live born, fetal death/stillborn, miscarriage, pregnancy termination and reason for termination (also consider time trends and geography) and termination for a fetal anomaly)
Sex
Obstetric complications (e.g., preeclampsia, premature delivery)
Pregnancy order (singleton, twin, triplet)

Fetal/Neonatal Outcomes
Anomalies diagnosed at birth or termination (including autopsy results)
Anomalies diagnosed after birth
Weight at birth indicating whether small, appropriate, or large for gestational age
Length at birth
Head circumference at birth indicating whether small, appropriate, or large for gestational age
Condition at birth (including, when available, Apgar scores at 1 and 5 minutes, need for resuscitation, admission to intensive care nursery)
Neonatal illnesses/complications, hospitalizations, drug therapies
Genetic testing results if performed

Follow-up
Source of information (e.g., pediatrician, mother)
Date of receipt of information
Anomalies diagnosed since initial report
Developmental assessment
Infant illnesses, hospitalizations, drug therapies
Breastfeeding exposure