Guidance for Industry

Establishing Pregnancy Registries

DRAFT GUIDANCE

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

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Draft - Not for Implementation

Guidance For Industry[1]

Establishing Pregnancy Registries

I. INTRODUCTION

This guidance is intended to provide sponsors with guidance on establishing registries on pregnancy outcomes from exposures to specific medical products. A pregnancy registry is a systematic epidemiology study that involves collecting and assessing postmarketing data on the potential for adverse health effects to the mother, fetus, and/or live-born infant from exposure to drugs, biologics, vaccines, or other exogenous products during pregnancy. Registries can provide useful information that can be included in product labeling. The guidance focuses on establishing a registry to assess suspected or unknown risks to pregnancy outcomes. A pregnancy registry design as described in this document is not appropriate for products (e.g., tretinoin or thalidomide) where the goal is to monitor and evaluate programs intended to prevent pregnancy exposures.

II. BACKGROUND

For the majority of products, whether newly marketed or commercially available for an extended period of time, laboratory animal studies and isolated case reports may provide the only information on potential health effects during human pregnancy. Randomized, controlled studies of health effects during pregnancy require the deliberate administration of products to pregnant women and are often infeasible (Mastroianni et al., 1994). During clinical development of most products, pregnant women are actively excluded from trials, and, if pregnancy occurs during a trial, the usual procedure is to discontinue treatment and drop the patient from the study. Consequently, at the time of a product's marketing, there are seldom meaningful human data on the effects of that product during pregnancy. However, depending on the indication and characteristics of the patient population, women may be exposed inadvertently to a given product

[1]This guidance has been prepared by the Pregnancy Registry Working Group of the Pregnancy Labeling Taskforce, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on establishing pregnancy registries. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

prior to recognition of their pregnancy, or they may be exposed to the product during a recognized pregnancy. To estimate the potential extent of exposure of pregnant women to any particular product, it can be assumed that approximately 11 percent of women between the ages of 15 and 44 will become pregnant annually. This pregnancy rate varies considerably by age group and ranges from 1 to 18 percent per year (Ventura et al., 1992 and Forrest et al., 1990). Clinical recognition of pregnancy typically occurs by 8 weeks after the last menstrual period (post-LMP) (Danforth et al., 1986), but considerably longer periods of time can elapse before knowledgeable prenatal healthcare providers evaluate exposed pregnancies. Approximately 60 percent of pregnancies are unintended (Forest 1990 and Westoff 1988), rendering it unlikely that potentially adverse exposures would be avoided in these pregnancies prior to their clinical recognition. Consequently, the patterns and extent of exposure to drugs or biologics often do not differ between women of childbearing age and those in the first trimester of pregnancy (Weiss et al., 1997). For chronic conditions requiring ongoing treatment, some exposures will continue even after clinical recognition of the pregnancy. Because of these patterns of exposure during pregnancy, the Food and Drug Administration may ask the sponsor of an approvable product to provide data on the potential risks of that product in human pregnancy under a phase-4 commitment. Alternatively, the sponsor of a marketed product may wish to obtain additional data on potential risks and negative findings associated with the use of the product in human pregnancies to update the product labeling.

Although there are several sources for relevant postmarketing data on pregnancy outcomes, these sources have their limitations. *Spontaneous reports* are inherently retrospective, and although they may be useful in identifying clusters of distinct rare outcomes, because of their potential for bias, they should not be used alone to identify increases in prevalence rates of adverse events. *Epidemiology studies,* such as cohort studies and case control studies, have a potential for bias in patient selection and in ascertaining outcomes and exposures. When well conceived and well conducted, these studies can provide data sources of adequate size to examine relatively rare events. *Population-based surveillance* systems can experience under-reporting of outcomes and do not link specific maternal exposures to fetal anomalies (Rosa 1992).

Pregnancy registries are recognized as one method for ascertaining major risks associated with a drug or biologic exposure during pregnancy. For products known to adversely affect pregnancy outcomes or the developing fetus, the registry model may be used to estimate the magnitude of risk. A registry may also be used to identify factors that modify risk and to identify and quantify long-term effects such as delayed development, other neurological impairments, or any effects that might be detected in older children previously exposed in utero.

This guidance on establishing pregnancy registries should be used in conjunction with other epidemiological literature for information on the design, conduct, and interpretation of

observational studies.[2] Because the development of pregnancy registries requires specialized knowledge in a variety of areas, the sponsor of any registry is encouraged to obtain advice from experts in the fields of pharmacology, embryology, teratology, obstetrics, and epidemiology when designing the registry.

III. PREGNANCY REGISTRIES

A pregnancy registry is a systematic epidemiology study that involves collecting and assessing postmarketing data on the potential for adverse health effects to the mother, fetus, and/or live-born infant from exposure to drugs, biologics, vaccines or other exogenous products during pregnancy. Pregnancy registries originated because of the limitations of other data sources, such as spontaneous reporting systems and birth defect registries. They differ considerably from these other systems in both design and methodology.

A pregnancy registry collects and analyzes reports of pregnancies exposed to a product or agent and actively obtains follow-up information on these pregnancies including outcome of the pregnancy and the infant. Voluntary reports are elicited from patients and healthcare providers with registration in the registry based upon both identification of pregnancy and documentation of exposure at some time prior to and/or during pregnancy. At the time of registration, information is collected on the drug exposure, maternal disease status, and other factors that may affect pregnancy outcome. For prospective reports, pregnancies are followed and outcomes may be obtained using a variety of approaches, including mailed questionnaires, maternal interviews, medical record abstraction or a combination of these methods. Registries should be designed to obtain information on the risk of a product to the mother and child with an expected time frame for completion. The design of each pregnancy registry should take into account the epidemiology, natural history, and current medical management of the maternal disease being treated; the pharmacological properties of the product, and what is known about the teratogenicity of the product.

Outcome rates among registry participants are compared to rates among women without the exposure of concern. The selection of an appropriate comparison group is critical to the interpretation of results and must be made cautiously, as no one comparison group is appropriate for all studies.

If adequately designed and executed, pregnancy registry studies can provide evidence to rule out or confirm suspected risks, quantify risks, or identify factors that affect the risk of adverse

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[2] ISPE "Guidelines for Good Epidemiologic Practices for Drug, Device and Vaccine Research in the United States," *Pharmacoepidemiology and Drug Safety*, 1996; 5:333-338. In addition, a draft guidance for reviewers entitled *Review of Human Pregnancy Outcome Data* is being developed and should be available in June 1999.

outcomes, such as dose, timing of exposure, or maternal characteristics. Similarly, for products known to be harmful during pregnancy, registries can supplement other efforts to monitor effectiveness of pregnancy control programs, quantify risks, and identify factors that increase or mitigate risk (e.g., dose, timing of exposure, maternal disease).

IV. WHEN IS A PREGNANCY REGISTRY NEEDED?

The decision to establish a registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the study. The evaluation of the need for a registry should take into account the actual or expected use of the product in women of childbearing potential and the perceived level of risk based on animal studies or prior information on the subject or similar products. Evaluation of the feasibility of completing the study should take into account the expected patterns of product use relative to fetal development, what outcomes are expected, and how these outcomes are identified.

Pregnancy registries are particularly important for products with a high use pattern in women of childbearing age because they are used to treat either chronic medical conditions or conditions with a high incidence in women. These may include, but are not limited to, anti-infective agents, antidepressants, anti-epileptics, and anti-asthmatics. Pregnancy risk information, particularly comparative information, is critical for products indicated for medical conditions that are caused or exacerbated by pregnancy such as asthma, diabetes, and hypertension. Pregnancy risk information is also important for products used in the treatment of conditions associated with high morbidity or mortality where treatment cannot be discontinued during pregnancy, such as some anti-infective or antiepileptic agents.

Pregnancy registries may also be useful to evaluate products suspected of causing harm during pregnancy based on animal reproductive toxicology studies, structure-activity relationships, pharmacological class, or human case reports.

The following criteria can be used as a guide to evaluate the need for a pregnancy registry study for a particular product or class of products:

- Live, attenuated vaccines or other products with the potential to cause subclinical infection in the mother

- Any product expected to be used commonly by women of reproductive potential (i.e., especially new molecular entities)

- Products continued during pregnancy because they are necessary for conditions associated with high morbidity or mortality

- Products suspected of adverse effects in human pregnancy based on structure, pharmacologic activity, pharmaceutical class, findings from laboratory animal studies, or spontaneous human case reports

- Products known to be harmful if used during human pregnancy, but for which the magnitude or other risk characterization is unknown

Pregnancy registries are unlikely to be requested in the following situations: (1) there is no systemic exposure, (2) the product is not intended for use in women, or (3) the product is not intended for use in women with reproductive potential.

V. WHEN SHOULD A REGISTRY BE ESTABLISHED?

Ideally, a pregnancy registry should be established as early as possible after a new product is deemed approvable, either before or at the time of entry into the marketplace. This will allow early identification of major risks and facilitate labeling changes to reflect these risks. The need for implementation of control programs to minimize identified risks may then be addressed as well.

Based on historical patterns of spontaneous reporting, registry recruitment efforts are expected be most fruitful in the first 5 years of marketing when prescribers most carefully scrutinize the risks and benefits of a new product. Prospective reports of inadvertent exposures will be most frequent when little is known about the adverse health effects of a new product during pregnancy. After the product has been marketed, more pregnancy risk estimations and information may be available from the medical literature, but this does not rule out the potential need for registries of older products or comparative registries of old and new products.

Recruitment efforts for a pregnancy registry should be made to ensure enrollment of a heterogeneous study population. Variations in demographics, severity of maternal disease, timing of exposure, dose, length of treatment, and other differences among study participants may help identify factors that modify adverse effects and distinguish subgroups of women at particularly high risk. Recruitment efforts targeting patients with differing demographics and medical conditions as well as their healthcare providers in the public and private sectors may help to obtain such heterogeneity.

Expanding the scope of registries to include domestic and international reports can also be beneficial. International studies are logistically complex and require special expertise to interpret country-specific differences in languages, medical practices, and rates of therapeutic abortions. Despite such complexities, the larger study size and population heterogeneity afforded by

international studies can provide valuable information; thus, the feasibility of carrying out such studies should be carefully considered.

VI. WHAT DOES A WELL-DESIGNED REGISTRY LOOK LIKE?

It is recommended that all pregnancy registries include a carefully developed, formal written protocol to ensure consistency of methods used in data collection and analysis. The principles of epidemiologic research, and those of observational research in particular, apply to the design and conduct of a pregnancy registry. Some of these principles are discussed in the 1996 ISPE guidance on such studies. Only those methodological issues that are characteristic of, or particularly critical to, pregnancy registries will be described here.[3] Because pregnancy registries are observational, they require well-documented and consistently applied procedures from recruitment to interpretation of study results to avoid introducing factors that might bias the conclusions of the study. Suggestions for avoiding some of the biases especially critical for the design and conduct of registry studies are discussed below.

A. Background Information

When developing the protocol for a registry study, the background section of a registry protocol should summarize findings from reproductive toxicity studies in laboratory animals, relevant pharmacological and toxicological studies, and any available human data such as spontaneous reports or earlier human studies. The background information section should be more detailed than a typical product label and be understandable to a nonspecialist healthcare provider. Laboratory animal studies should be summarized and conclusions drawn as to whether findings are indicative of potential risk to human pregnancy. If a potential risk is considered to exist, then this potential risk should be described in as much detail as possible.

Known prior human pregnancy exposures should be described in terms of time of exposure, maternal adverse events, pregnancy outcomes, and the type of report, from a clinical trial or spontaneous reports. If information is available for products in the same therapeutic class or products with similar pharmacological properties, these findings and their potential relevance to the sponsored project should be included. Existing human data should be interpreted in terms of whether risk from exposure during pregnancy is unknown, uncertain, suspected, or certain.

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[3] Textbooks in epidemiology and survey research methods are also available, as are articles in the medical literature that provide excellent reference material on observational study design and methodology.

The characteristics of the patient population expected to use the product should be described in terms of the number and proportion of all women with the labeled indication by age group. If the potential for off-label use exists, these numbers should also be carefully estimated. An annual estimate of product exposure should be calculated for all women of childbearing potential and for pregnant women. Any assumptions made when calculating these values should be clearly stated and the best-case and worst-case scenarios discussed.

In addition to the potential numbers of pregnant women exposed to the product, the impact of the medical condition being treated on the pregnancy outcome should be described. The expected characteristics of exposure during pregnancy (dose, timing, duration), and the likelihood that the treatment would be discontinued at recognition of pregnancy should be discussed. The sponsor may decide to develop these expectations in consultation with a variety of experts.

B. Description of Research Methods

1. Patient recruitment

Enrolling an adequate number of pregnant women with exposures of concern into a pregnancy registry means using an active recruitment strategy. Recruitment strategies may include an announcement of the registry and contact numbers in the product label with similar notices in the product circular, promotional materials, and product Internet pages. Other recruitment efforts might include announcements in professional journals, women's magazines, professional and maternal/infant advocacy group newsletters and Internet sites, personal mailings to specialists, lectures, and information booths at professional society meetings. Sponsors are encouraged to work together and with the FDA, the Centers for Disease Control and Prevention (CDC), Organization of Teratogen Information Services, and other similar organizations to maintain and disseminate lists of any ongoing pregnancy registries to promote awareness among healthcare providers and the public.

The study protocol should include scripts that will be used for registry announcements, to recruit patients into the registry and to provide answers to questions anticipated from responding healthcare professionals and patients. Accurate, current information on what is known about the product and its use during pregnancy should be presented in a clear and timely manner upon first contact with the patient or healthcare provider.

Although information about ongoing pregnancy registries and recruitment announcements may be included in promotional materials, it is important that they not promote use of the product during pregnancy. All such materials and texts should be discussed with and reviewed by the appropriate new product review division or office at FDA and the Division of Drug Marketing and Communications (DDMAC) in CDER or the Advertising and Promotional Labeling Staff in

CBER prior to implementation of the study, and subsequent content changes to these materials should also be cleared through CDER and CBER, respectively.

Some pregnancy registries have relied solely on recruitment of reports from healthcare professionals who provide exposure and outcome information without the knowledge or consent of the patient (White et al., 1997). There are several drawbacks to this approach. First, healthcare professionals may not be highly motivated to complete questionnaires resulting in a substantial loss to follow-up. The healthcare provider may have a real or perceived medical, legal, or ethical conflict of interest if he or she were the one to prescribe the product of exposure, or they simply may be reluctant to seek out and disclose confidential information on pregnancy outcome without maternal consent. Finally, exposures during pregnancy are most commonly reported by prenatal healthcare providers, yet these same individuals know little about the infant outcome after delivery. Thus, relying on birth certificates (Watkins et al., 1996) or prenatal providers could yield incomplete and potentially misleading information.

Other registries recruit and enroll pregnant women directly and obtain informed consent prior to registration (Holmes 1998). Registries conducted in this manner have had excellent recruitment with minimal losses to follow-up. Maternal telephone interviews are conducted at several intervals after registration to identify early outcomes, such as spontaneous abortions and elective terminations, and shortly after delivery to obtain information on the health status of the infant. With maternal consent, medical records can be obtained for cross-validation and pediatricians contacted to verify the health status of the infant. Maternal and infant medical record review and pediatrician follow-up are the preferred methods for continuing pregnancy outcomes in registries. The degree of record review will depend on the outcome of interest. The text of the informed consent form should be included with the study protocol and should be cleared in conjunction with the study protocol by an appropriate institutional review board(s). Whether all pregnancy registry studies require informed consent and IRB review is an unsettled question, but these measures are highly desirable in ensuring the collection of informative data that will withstand scientific scrutiny and protect the patient's right to privacy.

2. *Eligibility requirements*

Women should be enrolled in a registry after exposure to a product prior to and/or during pregnancy, but without knowledge of the outcome of pregnancy. If the status of the pregnancy has already been assessed through prenatal testing (e.g., targeted ultrasound, amniocentesis), such reports are usually considered retrospective. The inclusion of such reports in the database could conceivably bias the study towards the recruitment of women at higher or lower risk of an adverse pregnancy outcome. Limiting enrollment to women recruited within the first trimester of pregnancy or prior to prenatal testing may help to reduce or eliminate this bias. Caveats to this recommendation, however, would be for cases where the suspected critical exposure period is in

the later trimesters (discussed later in the analysis section) or when the product is specifically initiated later in pregnancy.

Information from such ineligible patients may nonetheless provide useful information. For example, retrospective reports of infants born with a specific constellation of anomalies may be combined with similar cases in the registry and evaluated as a case series. Thus, the sponsor may choose to follow-up reports of patients otherwise ineligible for the registry study. If so, this should be specified in the study protocol, and results from these patients should be summarized in the Other Human Reports section of the study report. Information obtained from patients determined to be ineligible upon recruitment should not be included in the study results section nor used to calculate event rates.

With active recruitment of patients into a pregnancy registry, a heterogeneous collection of reports can be anticipated. Commonly, a mixture of prospective and retrospective reports will be received in spite of the desire for enrollment prior to knowledge of the outcome. These reports should come from individuals with varying levels of medical expertise and should include a spectrum of conditions and outcomes ranging from the clearly important to the trivial. Careful consideration needs to be given a priori to the information to be collected at first contact, the source of that information, how eligibility status will be determined, and the disposition of information from ineligible patients.

Sponsors are required to report spontaneous reports of serious adverse outcomes, such as birth defects, to the FDA when identified during the recruitment process even if such reports are not included in a pregnancy registry analysis (21 CFR 314.80). However, these reports should be identified as having been reported to the registry. Waivers of the specific time frames and methods for this requirement with proposed alternative reporting plans may be requested for individual registries.

3. Data collection at enrollment

Once eligibility is determined and the patient consents to enroll in the study, baseline information on the patient, her pregnancy, the drug exposure, and medical conditions should be collected. A list of suggested minimal data elements to be obtained for each pregnancy exposure is provided in Attachment 1. What is collected and the source(s) of information depend on a variety of factors and should be modified appropriately for the specific condition or exposure under study. Because a variety of genetic, behavioral, and environmental factors can influence the risk of an adverse pregnancy outcome, these should be collected in as complete a manner as possible. Care should be taken to ensure that the information is ascertained in an unbiased manner. At minimum, data elements should include product exposure information, such as product, dose, duration, dates of administration; maternal information, such as age, obstetrical history, medical history, current medical conditions; behavioral factors, such as cigarette smoking, alcohol use, and illicit drug use;

and environmental factors, including maternal and paternal occupation, and residence. Although much of this information can be elucidated upon interview with the mother, medical record abstraction or an interview with the patient's primary healthcare provider is strongly recommended to confirm information obtained by interview.

Information that can usually be collected immediately upon enrollment includes the patient's name and contact information, her healthcare provider(s) and their contact information, the date of the last menstrual period (LMP), and the estimated delivery date. Exposure information should be obtained on all medical products that the mother used including the product under study, concomitant medications, and over-the-counter medications. (See Attachment 1.)

4. Patient follow-up

Throughout the entire pregnancy, additional contacts should be made with the patient, and in some cases with the healthcare provider, to obtain updated exposure and risk factor information, capture the results of any diagnostic testing, and identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. The study protocol should state the number, frequency, and timing of follow-up contacts, how contact will be made (mail, telephone) and data to be collected at each contact. The rationale for the follow-up mode and schedule should be explained in the study protocol.

The frequency of follow-up contacts and the amount and level of detail of information may vary by study design, the number of enrolled women, and the expected outcomes. The number and frequency of contacts should also balance the burden to the patient with the desire to collect precise and detailed information on exposure and risks.

It is critical that all of the women enrolled in the study are followed in the same manner, regardless of their characteristics. Losing track of a particular subgroup of women, if the reason they are lost is in some way related to their pregnancy outcome, can bias the study results. Additionally, losing a large proportion of study participants will invalidate an otherwise well-designed registry. Obtaining information from the woman at enrollment about how to contact several close friends and relatives may help in maintaining contact with her throughout the study.

5. Study outcomes

The specific outcomes that should be measured will vary depending on findings of concern from laboratory animals and humans and characteristics of the patient population. A minimal list of outcomes that should be collected includes maternal adverse events, labor and delivery complications, and major categories of pregnancy outcomes including spontaneous abortion, elective termination, fetal death/stillbirth and live born infants. However, the types of outcomes and the level of detail may vary from study to study, depending on characteristics of the study

product. Detailed case definitions of all outcomes to be measured and how they will be assessed should be specified in the protocol.

Any congenital anomaly found in each of the major categories of pregnancy outcomes should be recorded routinely. To detect an increase in anomalies incompatible with life, it is important to obtain information on autopsy results from late fetal deaths and stillbirths. Similarly, fetal pathologic evaluations may help confirm diagnostic test results for elective terminations made after a diagnosis of a fetal anomaly.

Upon a live-birth delivery, minimum information that should be collected includes date of birth, length of pregnancy, birth weight and length, sex of the infant, major and minor anomalies identified at birth, and whether a single or multiple birth occurred. For multiple births, this information should be collected for each infant along with the birth order. Based on the product(s) under study, consideration should be given to collection of more common neonatal conditions such as hyperbilirubinemia, apnea, and conditions related to prematurity.

Outcomes can be obtained using a variety of approaches, including mailed questionnaires, maternal interviews, medical record abstraction, or a combination of these methods. Most of the critical information can be obtained from timely mail or telephone interviews of the mother, obstetrician and pediatrician, medical record abstraction, and birth record review. An important consideration is the feasibility of obtaining outcome information by self-report, medical record review, and observations normally made by the obstetrician and pediatrician before and after birth.

In studies where the expected outcomes are difficult to detect without expert evaluation or require some time to manifest, more in-depth follow-up may be recommended. Specialist examinations or diagnostic testing of all live births may help with the identification of some minor anomalies. Similarly, long-term follow-up of infants may help detect neurological, behavioral, or developmental abnormalities that do not manifest until later in infancy or childhood.

6. *Selection of a comparison group*

Selection of an appropriate comparison group is one of the most important and difficult decisions to make in designing a registry. If the condition being treated by the study product is associated with an increased risk of adverse pregnancy outcome (e.g. depression, epilepsy, hypertension), comparison to a healthy population without this condition may result in bias. Similarly, if the medical condition being treated occurs more frequently among women with certain risk factors that increase the possibility of adverse outcome (e.g., older age, obesity, smoking, poor diet), then comparison to the general population of pregnancies would be inappropriate. If the condition being treated by the study product is not associated with adverse pregnancy outcome, a suitable comparison group could be one with exposure to a product considered to be without risk during

pregnancy. The group of women exposed to the product without risk should have relatively similar characteristics as those exposed to the study product.

Unexposed women can be used for comparison provided they have similar characteristics to those exposed to the study agent. Examples of such comparison groups are pregnant friends or neighbors of the exposed woman, or those being treated by the same obstetrician. As there is usually no ideal comparison group, inclusion of more than one comparison group can substantially add to the power of the study to detect or rule out risks. Estimates of adverse pregnancy outcome rates from the general population should only be used in conjunction with at least one study-specific comparison group as described above. Because of data collection differences and secular trends in medical care, historic controls are not recommended and should not be used in lieu of a study specific comparison group.

7. Statistical considerations

Determination of an adequate sample size to detect a significant effect of exposure during pregnancy takes an understanding of the background levels of pregnancy outcome in the general population as well as what might be anticipated in an appropriate comparison group to the study population. To estimate sample size, it can be assumed that approximately 15 percent of clinically recognized pregnancies will end in spontaneous abortion by 20 weeks post-LMP; approximately 20 percent to 30 percent of pregnancies will end in elective termination; 3 percent in fetal death/stillbirth after 20 weeks post-LMP; and the remainder in live births (Ventura et al., 1992). These population estimates vary considerably by age and specific values should be obtained within the 15 to 44 year range if relevant for the patient population. Major congenital malformations occur in approximately 2 percent to 4 percent of live born infants and minor malformations in 14 percent to 22 percent (March of Dimes 1996).[4] Individual major malformations can occur in 1/1000 to 1/10,000 live born infants (Oakley 1986) and 20 percent of infants with one or more minor congenital anomalies have a major birth defect (Leppig et al., 1987). Sample sizes sufficient to detect a clinically significant difference (typically a doubling or tripling of the outcome of concern) with 80 percent power at the 0.05 level of significance are usually calculated and are provided in Attachment 2. These sample size calculations will be relevant only to prospective reports. If the outcome of concern occurs only in live born infants, it is important to consider that these may only represent approximately 50 to 60 percent of all prospectively enrolled pregnancies, considering the expected prevalence of spontaneous abortions, elective terminations and fetal deaths/stillbirths. In reporting results from pregnancy registries, the power of the study to detect the outcome of concern based on the existing sample size for prospective reports should be specified.

[4] See also Oakley 1986 and Petrini et al., 1997.

8. Methods of data analysis

If women who used the study drug late in pregnancy are recruited into the registry, they should only be compared to women who continued their pregnancies into the same time period and not to women who had spontaneous or therapeutic abortions before they reached that stage of pregnancy. This can be accomplished by stratification or survival analysis in which each pregnancy is split into equal-length time periods and outcome rates calculated for each stratum.

Following stratification by pregnancy outcome (live birth, spontaneous abortion, elective termination), reports should be stratified further into prospective and retrospective status and then maternal and fetal outcomes analyzed separately. The total number of prospective reports received and the proportion with outcome known, outcome pending or lost to follow-up should be given. Criteria used to classify reports that are pending or lost to follow-up should be specified in the protocol.

Those prospective reports with outcome known should then be further stratified according to whether the outcome was a spontaneous abortion, elective termination, fetal death/stillbirth or live birth. Proportions should be calculated by placing the number of each outcome in the numerator and the total number of prospective reports with outcome known in the denominator. Each outcome category should be described in detail in terms of whether any fetal abnormality (e.g., structural malformation, chromosome aberration, or pathologic change) or outcome of concern occurred, and proportions for these calculated with the appropriate denominator. It is likely that products of conception from first trimester spontaneous abortions and elective terminations will not have been examined for abnormalities. These outcomes should be stratified according to whether they occurred in the first or second trimesters. The 95 percent confidence interval for each proportion should be calculated, and statistical comparison to the reference group made when there are sufficient data to ascertain whether the outcome of concern occurred at a higher or lower level than expected.

Given the heterogeneous nature of data obtained in pregnancy registries, there is no one format for data presentation that is applicable for all studies. Appropriate categorization of congenital anomalies is complex, and experts should be consulted in this effort. The choice of a final format depends on outcomes identified in the study protocol, unanticipated findings, and expert advice. Sponsors are encouraged to develop forms of data presentation and analysis that fully capture outcomes of concern within their particular study.

VII. REPORTING RESULTS

Reporting of adverse events noted from pregnancy registries is not specifically addressed by Federal regulations and, although they are postmarketing surveillance studies, the current

recommendations from FDA, Office of Postmarketing Drug Risk Assessment are that pregnancy registries requested by the product's sponsor are subject to FDA 15-day alert reporting of serious and unexpected adverse drug experiences in addition to periodic reporting of nonserious and labeled adverse events as specified under 21 CFR 314.80 (18) and 310.304 and 600.80. A sponsor may apply for a waiver from these regulations.[5] Exceptions are when the sponsor is not involved in the pregnancy registry and when adverse event reporting is not required by the FDA but is certainly welcomed as voluntary reporting of the adverse event. Voluntary reporting can be done via MedWatch, the FDA medical products reporting program (telephone 1-800-FDA-1088, FAX 1-800-FDA-0178).

Methods of data presentation and analysis specified in this guidance document should be reported in interim and annual reports to the product new drug application (NDA) or product license application (PLA) in addition to submission of the final report of the pregnancy registry findings. The format of these reports will depend on the audience (medical literature) and/or the requirements set forth by the organization funding the study and the product sponsor's role in the registry's development and conduct.

Final or comprehensive report(s) should include data analyses or descriptions (such as a case series) where analysis is not possible or inappropriate for each of the groupings or substrata of reports such as live birth/spontaneous abortion/elective termination reports, prospective/retrospective reports, and fetal outcomes. Where data analysis is performed, the power of the study to detect the outcome of concern based on the existing sample size for prospective reports should be reported.

The following is a list of minimal information that should be provided in interim reports from pregnancy registries. These results should be accompanied by a descriptive summary of progress to date and an interpretation of findings:

1. Total number of women enrolled to date; number (%) retrospective reports; number (%) prospective reports and proportion with outcome known, pending or lost to follow-up

2. For prospective reports with known outcome:

   - demographics, obstetrical and medical history of mothers and maternal adverse events

   - proportion of spontaneous abortions (spontaneous loss up to 20 weeks post-LMP in clinically recognized pregnancies. Stratify according to occurrence in the 1st or 2nd trimester).

[5] See 21 CFR 314.90 for information on waivers.

- proportion of elective terminations (elective termination at any interval during pregnancy; stratify according to occurrence in the 1st or 2nd trimester)

- proportion of fetal death (death of the fetus at ≥ 20 weeks post-LMP). This proportion can be combined with stillbirths as these outcomes can be difficult to separate.

3. For prospective reports of spontaneous abortions and elective terminations:

   - proportion with abnormalities in products of conception; stratify according to occurrence in 1st and 2nd trimesters. Identify the exposure interval and comment on any notable features of cases (e.g., history of repeated spontaneous abortion).

4. For prospective reports of fetal death/stillbirths:

   - proportion with abnormalities in products of conception; stratify according to occurrence in 2nd and 3rd trimesters. Identify the exposure interval and comment on any notable features of each case (e.g., maternal diseases, types of examinations).

5. For prospective reports of live born infants:

   - proportion with abnormalities of concern, proportion with low birth weight (< 2500 gm), proportion with pre-term delivery (< 37 weeks), proportion small for gestational age

VIII. OTHER CONSIDERATIONS AND ADDITIONAL STUDIES

Pregnancy registries provide a potential means of obtaining meaningful data on major risks associated with exposures during pregnancy. Reports can be obtained from large geographic areas and heterogeneous populations can be surveyed. When conducted in the first years after marketing, an estimate of major risks, if any, can be rapidly obtained and appropriate control programs implemented. As all registries are based on voluntary reporting for identification of exposed pregnancies, however, referral bias is a common, unavoidable element to be taken into consideration. It will be impossible under most circumstances to ascertain the total population of women exposed to a product during pregnancy, or to assess whether the sample of pregnancies reported to registries is at higher or lower risk for adverse outcomes than the remainder of pregnancies not reported from the exposed population. The problem of referral bias can be ameliorated by choosing an appropriate comparison group and by broad, rigorous recruitment, but referral bias cannot be completely eliminated.

For these reasons, consideration should be given to the conduct of additional studies using alternative approaches. This will be particularly important to confirm findings from pregnancy registries and to follow up any outcomes of concern identified from registries. In many situations, case control studies will be most appropriate. Another possibility is to develop better methodologies for evaluating adverse health effects during pregnancy using automated databases existing in health maintenance organizations (HMOs) and Medicaid. Use of automated databases should permit surveillance of large segments of the population with a known denominator for exposures during pregnancy. It should be possible to identify pregnancies from the time of first clinical recognition to capture information on all major outcomes (spontaneous abortions, elective terminations, fetal deaths/stillbirths and live born infants) from automated databases. Ideally, automated databases should link mothers to their infants to enable the long-term detection of postnatal sequelae. Use of automated databases alone at the time of initial product marketing would not be practical as it is unlikely there would be a sufficient number of exposed pregnancies to design a study with sufficient power to detect most outcomes of concern.

Pregnancy registries are the most feasible study designs to employ at the time of first marketing, with follow-up studies as needed to confirm and clarify findings. It is expected, however, that data from well-designed and -conducted pregnancy registries will provide data for inclusion in product labeling and package inserts to guide clinicians who seek guidance in ascertaining risks to the pregnant woman and her fetus associated with exposure to a given product.

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ATTACHMENT 1

Suggested Data Elements For Pregnancy Registries

A. General

Name of reporter at initial contact with registry:
Date of initial contact with registry:
Telephone number of reporter:

B. Maternal Information:

Birthdate:
Race: African-American/Hispanic/Asian/Caucasian/Other
Maternal Product/Drug Exposure (Product/Drugs of interest/study):

1. Name of Product/Drug & formulation:
   Dosage:
   Route:
   Date of first use: (Gestational age exposure)
   Date of last use/continuing: (Repeat for number of times taken)
   Indication:
2. Product/Drug: (etc.)

Other Maternal Medications (List):
Dosage: Date of first use: Last use:

Obstetrical History:
Number of pregnancies
Full-term deliveries:
Premature deliveries:
Spontaneous abortion:
Elective terminations
Previous fetal/neonatal abnormalities: yes/noSpecify:
Date of Last Menstrual Period:
Complications, etc. during exposed pregnancy (specify date and complications):
Multiple fetuses: yes/no # of fetuses

Maternal Medical History:

Hypertension	Diabetes	Seizure Disorder
Thyroid Disorder	Heart Disease	Connective Tissue Disease
Hepatitis	Other:	

Family History (specify type, maternal/paternal, etc.):
- Spontaneous Abortions
- Anomalies/Malformations
- Multiple fetuses/births
- Occupation (maternal/paternal)
- Residence (maternal/paternal)

Maternal Recreational Drug Use:
Tobacco: #ppd @ LMP; #ppd currently
Alcohol: @ LMP; currently
Illicit Drugs (specify):

C. Neonatal Information:

Source of Information: Mother; Medical Record; Pediatrician; Obstetrician; Other
Date of Receipt of Information:
Live Birth: yes/no (If yes, proceed with the remainder of the form). If no, spontaneous abortion/stillbirth/elective termination? If stillbirth, congenital abnormalities detected? If elective termination, fetal test results and reasons for termination.
Date of Birth:
Gestational Age at birth: (in weeks); determined by: LMP/Ultrasound/Dubowitz exam
Birth Weight: lbs. Oz. (gms)
Length at birth: in. (cm)
Apgar scores: 1 min; 5 min
Physical Examination at Delivery:
- No dysmorphic features identified
- Minor anomalies (specify):
- Major malformation (specify):
- Syndrome/Diagnosis (specify):
- Other significant findings (specify):
- Other significant findings:

Examination by: Pediatrician; Family Practitioner; Nurse Practitioner; Other
Medications (dose, start date, end date, indication, etc.):

Follow-Ups:
Age: months
Date of F/U:
Weight: lbs. oz. (gms)
Length: in. (cm)
Physical Examination at F/U:
- No dysmorphic features identified
- Minor anomalies (specify):
- Major malformation (specify):

Syndrome/Diagnosis (specify):
Other significant physical findings:
Developmental Assessment: Normal; Possible Delay; Definite Delay
Specific Developmental Assessment (area of development, criteria/scale used, etc.):
Examination by: Pediatrician; Family Practitioner; Nurse Practitioner; Other
Medications (dose, start date, end date, indication, etc.):

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ATTACHMENT 2

Sample Size Determinations for Studies of Adverse Pregnancy Outcomes

Outcome	Denominator	Population Rate	Expected Increase Due to Exposure	Number of Exposed Pregnancies Needed*
Spontaneous abortion (miscarriage)	Enrolled pregnancies	15/100	100% (RR=2)	266
			200% (RR=3)	84
			300% (RR=4)	42
Low birth weight (<2500 grams)	Live births	10/100	100% (RR=2)	261
			200% (RR=3)	97
			300% (RR=4)	59
Fetal death or stillbirth	Live births plus fetal deaths	3/100	100% (RR=2)	684
			200% (RR=3)	236
			300% (RR=4)	136
Any major birth defects	Live births	3/100	100% (RR=2)	684
			200% (RR=3)	236
			300% (RR=4)	136
Specific Birth Defects				
Heart & Circulation	Live births	1/115	100% (RR=2)	2196
			200% (RR=3)	740
			300% (RR=4)	415
Genital & Urinary Tract	Live births	1/135	100% (RR=2)	2567
			200% (RR=3)	863
			300% (RR=4)	484
Nervous System & Eye	Live births	1/235	100% (RR=2)	4422
			200% (RR=3)	1481
			300% (RR=4)	827
Club Foot	Live births	1/735	100% (RR=2)	13695
			200% (RR=3)	4575
			300% (RR=4)	2544

Cleft lip with or without cleft palate	Live births	1/930	100% (RR=2)	17311
			200% (RR=3)	5778
			300% (RR=4)	3214
Stickler syndrome (or other rare birth defect)	Live births	1/10,000	100% (RR=2)	185539
			200% (RR=3)	61854
			300% (RR=4)	34367

*An equal number of pregnancies should be enrolled in each control group (unexposed or comparison drug.
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