Guidance for Industry

Establishing Pregnancy Exposure Registries

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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Clinical/Medical

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Establishing Pregnancy Exposure Registries[1]

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I. INTRODUCTION

This document is intended to provide sponsors with guidance on how to establish pregnancy exposure registries to monitor the outcomes of pregnancies exposed to specific medical products.[2] The guidance should be used in conjunction with other epidemiological literature on the design, conduct, and interpretation of observational studies (e.g., International Society for Pharmacoepidemiology 1996). Because the development of a pregnancy exposure registry requires specialized knowledge in a variety of areas, we encourage sponsors to obtain advice from experts in the fields of pharmacology, embryology, teratology, obstetrics, pediatrics, clinical genetics, and epidemiology when designing a registry.

The ultimate goal of pregnancy exposure registries is to provide clinically relevant human data that can be used in a product's labeling to provide medical care providers with useful information for treating or counseling patients who are pregnant or anticipating pregnancy (see Attachment A for examples of labeling). Such data can also be used to support a change from the originally assigned Pregnancy Category (e.g., acyclovir: Category C to B, budesonide inhalational powder: Category C to B).[3]

II. BACKGROUND

[1] This guidance has been prepared by FDA's Pregnancy Exposure Registry Working Group of the Pregnancy Labeling Task Force, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

[2] For purposes of this guidance, the term *medical products* means drugs and biological products, including vaccines.

[3] See 21 CFR 201.57(f)(6) for the content and format of the pregnancy subsection of labeling for prescription drugs, including the requirements for a statement regarding a product's pregnancy category.

Randomized, controlled studies of health effects during pregnancy require the deliberate administration of products to pregnant women and are often not feasible (Mastroianni et al., 1994). During clinical development of most products, pregnant women are actively excluded from trials, and if pregnancy does occur during the trial, the usual procedure is to discontinue treatment and drop the patient from the study, although her pregnancy is typically followed to term. Consequently, at the time of a drug's initial marketing, except for products developed to treat conditions unique to pregnancy, there are seldom meaningful human data on the effects of that drug during pregnancy.

For drugs used for preventive or active treatment in women of childbearing age, it is not uncommon for exposure to the fetus to occur during the critical period of organogenesis, because the woman was not aware of her pregnancy at the time. Approximately 10 percent of women between the ages of 15 and 44 become pregnant annually. This pregnancy rate varies considerably by age group and ranges from 1 to 18 percent per year (Ventura et al., 2000). About half of all U.S. pregnancies are unplanned (Colley et al., 2000).

Some women enter pregnancy with medical conditions that require ongoing or episodic treatment (e.g., asthma, epilepsy, hypertension). New medical problems may develop or old ones may be exacerbated by pregnancy (e.g., migraine headaches, depression). Studies have shown that most pregnant women use either prescribed or over-the-counter drugs during pregnancy (Bonati et al., 1990, De Vigan et al., 1999, Lacroix et al., 2000, Weiss et al., 1997).

Yet, even after years of marketing with accumulating experience in pregnant women, data in product labeling regarding risks of use during pregnancy rarely go beyond the data available at the time of initial marketing.

Historically, most information about risks of drugs in pregnancy has arisen from suspicious findings from spontaneous adverse event reports. This passive mechanism of surveillance has been well described (Kennedy et al., 2000). For identification of truly rare or unusual outcomes, this system offers many advantages. However, some of the well-known limitations of spontaneous reporting are particularly problematic when trying to evaluate drug risks in pregnancy. Limitations include the lack of denominator data, lack of controls, recall bias associated with retrospective reporting, barriers to reporting, and poor case documentation. These limitations can be overcome through use of prospective pregnancy exposure registries, which are recognized as one method for ascertaining major risks associated with a drug exposure during pregnancy.

III. WHAT IS A PREGNANCY EXPOSURE REGISTRY?

A pregnancy exposure registry is a prospective observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes.
Pregnancy exposure registries differ from other postmarketing surveillance techniques, such as birth defect registries and spontaneous reporting of adverse drug reactions, in that pregnant women are enrolled before the outcome of pregnancy is known. These other surveillance methods are

retrospective with enrollment typically based on an adverse outcome, such as an infant born with a birth defect, and risk factors are determined by looking backwards in time. Pregnancy exposure registries proceed from the point of drug exposure, however, so that a single registry can collect data on many pregnancy outcomes. This prospective orientation is an important feature — and the major strength — of the pregnancy exposure registry design.

Pregnancy exposure registries can:

- provide margins of reassurance regarding the lack of risk when a precise measure is impossible
- monitor for suspected risks raised by preclinical studies, premarketing clinical studies, or postmarketing case reports
- identify factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or maternal characteristics
- serve as hypothesis-generating tools

A pregnancy exposure registry ***is not*** a pregnancy prevention program.[4] Neither is it a mechanism to monitor and evaluate such programs.

IV. WHAT MEDICAL PRODUCTS MAKE GOOD REGISTRY CANDIDATES?

Animal reproductive toxicology studies are an essential tool for estimating potential risks of exposure to medical products in pregnancy. However, the positive and negative predictive values of such studies for humans are often uncertain (Mitchell 2000). Animal models can be misleading when screening for specific fetal effects by detecting associations that ultimately turn out to be false positive (e.g., hydrocortisone and clefts in mice) or false negative (e.g., thalidomide and no teratogenesis in rats) (Ward 2001). The strongest concordance between animal findings and human effects is when there are positive findings from more than one species, although even in this case the results cannot always be used to predict specific human effects or incidence in humans (Rogers et al., 1996).

Regardless of findings from animal studies, we recommend that a pregnancy exposure registry be seriously considered when it is likely that the medical product will be used during pregnancy as therapy for a new or chronic condition.

A medical product may also be a good candidate for a pregnancy exposure registry when one of the following conditions exist:

- Inadvertent exposures to the medical product in pregnancy are or are expected to be common such as when products have a high likelihood of use by women of childbearing age

[4] A pregnancy prevention program is a formal program of combined physician and patient education directed to avoiding pregnancy with the use of drugs with high absolute risk to the fetus but which are uniquely effective as therapy (e.g., isotretinoin), sometimes with restricted access to the drug (e.g., thalidomide) (Mitchell, 2000).

- The medical product presents special circumstances, such as the potential for infection of mother and fetus by administration of live, attenuated vaccines

The need for a pregnancy exposure registry increases when a medical product in one of the above categories may have the potential to cause harm during pregnancy. Information regarding potential harm can be based on one or more of the following:

- animal reproductive toxicology studies
- structure-activity relationships
- pharmacological class
- human case reports

Pregnancy exposure registries are unlikely to be warranted in the following situations: (1) there is no systemic exposure to the medical product, or (2) the product is not, or rarely, used by women of childbearing age.

V. WHEN SHOULD SUCH A REGISTRY BE ESTABLISHED?

A pregnancy exposure registry can be initiated by a sponsor at any time. The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. When the purpose of the pregnancy exposure registry is to assess margins of safety, to monitor for potential harm, or to detect safety signals, it is appropriate to initiate the registry as soon as possible, such as at the time of initial marketing, when a new indication is approved, or when patterns of use reveal that the product is used by women of reproductive age. In some cases, FDA may ask a sponsor to conduct an exposure registry under an IND before approval or, more typically, as part of a phase-4 commitment. A pregnancy exposure registry could also be started when there is a need to evaluate suspected risks raised by spontaneous adverse events reports or published case reports.

VI. WHAT SHOULD ONE CONSIDER WHEN DESIGNING A REGISTRY?

A pregnancy exposure registry's design should reflect its underlying objectives. These objectives can range from open-ended safety surveillance to testing a single specific hypothesis. The principles of epidemiologic research and those of observational research, in particular, apply to the design and conduct of a pregnancy exposure registry. Some of these principles are discussed in the 1996 International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States.

Thoughtfully developed, formal, written protocols ensure consistency of data collection and analysis. Pregnancy exposure registries should be based on well-documented and consistently applied procedures, from recruitment of an adequate number of participants to interpretation of registry results,

to avoid introducing factors that might bias the data. Because some fetal effects are relatively rare, even small or minor flaws in registry design and execution can have a large effect on the final results.

Consideration should be given to addressing the following critical elements in any pregnancy exposure registry protocol:

- objective(s) of the pregnancy exposure registry itself
- anticipated frequency of drug exposure during pregnancy
- comparison groups
- sample size to rule out a difference between the exposed and comparison groups at a predetermined level or to detect a predetermined level of risk; and how long it may take to enroll that number of women
- how to determine eligibility for enrollment
- source of information on drug exposure during pregnancy (e.g., health care provider, pregnant woman)
- congenital anomalies and other fetal effects of interest, including inclusion and exclusion criteria, and the time period for identification
- information to be collected related to an individual pregnancy outcome and the source of that information (e.g., mother, prenatal health care provider, infant's health care provider)
- disposition of data from protocol ineligible pregnant women
- methods to be used to assess risk including an analytical and statistical plan
- importance of an independent data monitoring committee
- importance of obtaining institutional review board (IRB) review and informed consent
- criteria for termination of the registry

To facilitate the eventual inclusion of data from the registry into the product labeling, we recommend that the appropriate premarketing and postmarketing review divisions at FDA be consulted to review the draft protocol.

A. Background Section of a Protocol

The background section of a protocol should describe why the registry is being conducted. Findings from the following should be summarized, along with conclusions regarding potential risks to human pregnancy:

- animal reproductive toxicity studies
- other relevant pharmacological and toxicological studies such as those that address structure activity relationships
- any available human data, such as spontaneous reports
- earlier human studies

The background section should also summarize the potential benefits of the product, especially if there are benefits unique or particularly relevant to pregnant women. We recommend that the characteristics

of the patient population expected to use the product be described in terms of the number and proportion of all women with the labeled indication by age group and that an annual estimate of potential product exposure in pregnant women be calculated. Any assumptions made when calculating these values should be clearly stated and the best-case and worst-case scenarios discussed.

In addition, the medical condition for which the product has a labeled indication and its impact on the pregnant woman and the fetus, should be described, including the effects of nontreatment. 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.

B. Description of Research Methods

1. Patient recruitment

To enroll an adequate number of eligible pregnant women, we recommend an active recruitment plan. A variety of strategies should be used to ensure as broad coverage as possible. Some strategies that have been used with moderate success by current registries include announcement of the registry and contact information in the medical product labeling; similar notices in the product circular, promotional materials, and product Internet pages; as well as announcements in lay and professional magazines, journals and newsletters; personal mailings to specialists; and exhibits at professional meetings. We encourage sponsors to work together and with FDA, the Centers for Disease Control and Prevention (CDC), the Organization of Teratogen Information Services (OTIS), and other relevant organizations such as patient advocacy groups (e.g., American Diabetes Association) and medical societies (e.g., American Rheumatology Society), to endorse or assist in the conduct of pregnancy exposure registries, thereby facilitating patient recruitment.

Recruitment materials should not actively promote an individual product's use in the special population of pregnant women, unless the package insert contains supporting information. Recruitment materials should not imply that product safety and efficacy information in pregnant women exists beyond the information contained in the currently approved labeling.

As with all other product-specific promotional materials, those related to pregnancy exposure registries are subject to 21 CFR 314.81(b)(3) or 601.12(f)(4) and, under those regulations, must be submitted to FDA at the time of first use. In general, any registry-related promotional materials and recruitment materials can be discussed with and reviewed by FDA prior to use, but such a review is not required. However, if the product is approved under an accelerated approval mechanism (21 CFR 314 subpart H or § 601 subpart E), submission prior to the time of first use is required (§§ 314.550 and 601.45).

2. Sources of baseline and follow-up information

We recommend examining all alternatives for obtaining information to determine the appropriate methodology based on, for example, the patient population involved, the suspected risk of the medication in pregnancy, and the number of enrollees needed.

a. Health care professionals as information sources

Most pregnancy exposure registries rely upon voluntary reports from health care professionals (e.g., Reiff-Eldridge et al., 2000). The advantages of using information obtained from health care professionals are convenience and less monetary expense because the medical sophistication of the source makes this method of obtaining information very efficient. However, there are several drawbacks to this approach.

- Health care providers may not be highly motivated to complete a questionnaire, so a substantial loss to followup may occur.
- A health care provider may have a real or perceived medical, legal, or ethical conflict of interest if (s)he prescribed the product, or (s)he may be reluctant to seek out and disclose information on pregnancy outcome without maternal consent, even when no specific patient identifiers are part of the collection.
- Exposures occurring during pregnancy are usually reported by the prenatal health care provider or by a specialist treating a specific condition in the mother (e.g., neurologist treating migraine); these providers often know little about the infant after delivery.

A variation of this method relies on the health care provider to obtain informed consent from the pregnant woman to acquire medical records from both the prenatal and pediatric providers.

Another model relies on spontaneous reports from both health professionals and patients (e.g., Goldstein et al., 1997, Shields et al., 2001).

b. Pregnant women as information sources

Some pregnancy exposure registries recruit and enroll women directly (e.g., The North American Pregnancy and Epilepsy Registry, 1998, Chambers et al., 2001). Typically, informed consent is obtained from the woman on enrollment. Recruitment of a motivated patient population can minimize loss to followup and provide more extensive information. Obtaining informed consent may confirm patient motivation and facilitate cross-validation of information reported by the woman by allowing for examination of medical records and interviews with the appropriate health care providers. However, a potential methodological problem with this approach is that the nonparticipation of patients who do not give consent can introduce selection bias. Also, obtaining information directly from pregnant women costs more as a result of the need for more intensive followups and medical validation of self-reports.

3. Selection of a comparison group

With a pregnancy exposure registry, a comparison group should be used to assess risk or provide a measure of assurance of safety. Comparison groups can be either internal to the study (e.g., defined and followed along with the exposed group of interest) or external to the study (e.g., information collected outside of the study by other investigators that is deemed relevant to the issue under

investigation). Registries may include both internal and external comparison groups, as varying findings between them can be instructive. The strategy for selection of an appropriate comparison group(s) should be made when designing the pregnancy exposure registry and included in the protocol.

Options for comparison groups include:

Internal:

- unexposed, concurrently enrolled pregnant women matched or stratified in relation to the exposed group to control for important covariates
- women within a multidrug registry (see section VI(B)(12) — multidrug pregnancy exposure registries) with a common indication or underlying risk factors who are not taking the medical product of interest

External:

- surveillance systems (e.g., from the National Birth Defects Prevention Network, the Metropolitan Atlanta Congenital Defects Program)
- background rates of grouped or individual outcomes (e.g., from the National Center for Health Statistics (NCHS), the International Clearinghouse for Birth Defects Monitoring Systems)
- other pregnancy exposure registries

Enrollment of a concurrent comparison group of unexposed pregnant women, while most desirable methodologically, may not be possible, and may exceed the scope of most registries. A background rate or the prevalence of congenital anomalies in a population based surveillance system or other pregnancy exposure registry may often be the only available comparator.

If background rates or information from a surveillance system are chosen as a comparison group, it is important to be aware of the limitations of whatever existing system is used (e.g., the National Birth Defects Prevention Network does not collect information on all congenital anomalies, NCHS may have accurate data on spontaneous abortions, but only on those requiring hospital care) so that appropriate analyses can be designed.

Additional considerations when choosing a comparison group from an existing system are the ascertainment methods used by the system, how outcomes are defined and identified, and the characteristics of the underlying population from which the cases are taken. The potential impact of any differences on the interpretation of data from the pregnancy exposure registry should be acknowledged and discussed in the protocol.

As there is usually no one ideal comparison group, we encourage the use of more than one comparison group to improve the validity of the registry.

4. Privacy and human subject protection issues

The importance of informed consent and use of an institutional review board (IRB) in the design of each pregnancy exposure registry should be considered, even for those registry designs thought to fall in the category of surveillance as opposed to a targeted study.[5] The protocol must comply with ethical principles and regulatory requirements involving human subjects research as specified in the federal regulations for the protection of human subjects (45 CFR part 46, 50, and 56). All pregnancy exposure registries should consult an IRB to ensure that the collection of data and all other procedures associated with the registry will withstand scientific and ethical scrutiny.

If informed consent is to be obtained from the patient, the text of the informed consent form should be included in the registry protocol. Pregnancy exposure registries are not designed to provide direct benefit and should not represent any risk to either the pregnant woman or the fetus; therefore, the decision to participate in the registry rests solely with the pregnant woman (see subpart B of 45 CFR part 46). If the registry seeks to obtain information on the child after birth either through physical examination (minimal risk) or medical record review (no risk), either parent may consent for the child (see subpart D of 45 CFR part 46).

5. Eligibility requirements

Women should be enrolled in a pregnancy exposure registry prospectively (i.e., after exposure to a product but 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 are usually considered retrospective. It is also desirable that women be enrolled who had drug exposure at the point in gestation with the highest risk of causing fetal effects. For congenital anomalies, this is most often the first trimester, but there are clearly drugs for which the suspected critical exposure period is in the later trimesters or for which the product is likely to be specifically initiated later in pregnancy.

Commonly, with active recruitment of patients into a pregnancy exposure registry, both prospective and retrospective reports will be received in spite of the desire for enrollment prior to knowledge of the outcome. It should also be anticipated that cases will be received where exposure is outside the time period of interest. The protocol should clearly delineate the disposition of all cases.

Because it may be difficult to obtain enrollment before prenatal testing on a consistent basis, to achieve an adequate sample size, some pregnancy exposure registries have included pregnancies with normal prenatal tests. However, inclusion of pregnancies with some a priori knowledge of normal outcome as prospective cases and exclusion of those with prenatal tests indicating a defect may potentially bias the results toward a lower overall defect risk (Honein et al., 1999).

If it is necessary to include pregnancies with some prenatal testing to achieve adequate numbers, then data analysis should address whether enrollment after prenatal testing biased the results.

[5] "Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health," 1997 (http://www.pharmacoepi.org/resources/privacy.htm).

6. Data collection

We recommend collection of the following baseline information on the patient once eligibility has been determined:

- patient identifier, and, if collecting data directly from the pregnant woman, contact information, including an alternative contact(s) if possible
- health care provider name(s) and contact information
- date of the last menstrual period and estimated delivery date
- exposure to medical product of interest, including dosage, route, and dates of administration
- medical indication for taking the product
- exposure information on all other medical products used, including prescription products, over-the-counter (OTC) products, dietary supplements, vaccines, and insertable or implantable medical devices
- other medical conditions

Attachment B provides a list of additional possible maternal and neonatal data elements to consider. 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 of interest. We recommend that data collection be as complete as possible, without sacrificing the quality of information for quantity of data.

If using an internal comparison group, for consistency, all information should be collected in an identical manner from both exposed and comparison group women. The registry protocol should include a detailed description of how information will be obtained. This description will help minimize variation. When information is obtained directly from the pregnant woman, we recommend a medical record abstraction or an interview with a patient's health care provider to confirm information obtained from the woman.

7. Patient follow-up

The objective(s) of the registry should determine the type, extent, and length of patient followup. The feasibility of obtaining reliable infant outcome information is a critical consideration in pregnancy exposure registry design. While prenatal health care providers are a good source of information on outcomes, such as spontaneous abortions, elective terminations, live births, and pregnancy complications, they are not a good resource for information on infant conditions not readily diagnosed at or soon after birth. The infant's health care provider is the best resource for full information on the health status of the infant.

Followup information can be obtained by:

- mailed questionnaires
- telephone interviews
- reviews of medical record abstractions
- reviews of birth records
- combinations of the above

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

We recommend the protocol also include:

- the number, frequency, and timing of followup contacts
- who will be contacted (mother, prenatal health care provider, infant's health care provider, other)
- how contact will be made (mail, telephone, other)
- how and what data will be collected at each contact

For consistency, pregnancies enrolled in the registry should be followed in the same manner. 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 registry results. Additionally, losing a large proportion of registry participants wastes resources and can invalidate an otherwise well-designed pregnancy exposure registry.

8. Pregnancy outcomes

Pregnancy outcomes include spontaneous abortions (loss before 20 weeks), elective terminations, fetal deaths/stillbirths (loss after 20 weeks) and live births. Within each of these categories the fetus or infant can be evaluated as to the presence or absence of anomalies or other fetal effects. We recommend that:

- The protocol specify *a priori* which pregnancy outcomes will be included and what fetal effects will be assessed as well as the inclusion and exclusion criteria (Holmes 1999) and measures of severity, if applicable, for congenital anomalies or other abnormalities of interest.
- The time period for ascertainment be designated
- A classification scheme such as the CDC birth defects code list[6] be used and specified in the protocol. The types of congenital anomalies or other fetal effects and the level of detail may vary, depending on the characteristics of the registry design. It has been suggested that grouping defects that share embryology and pathogenesis increases the likelihood that a teratogenic effect will be seen (Scheuerle et al., 2002).

[6] CDC. Metropolitan Atlanta Congenital Defects Program Procedure Manual, 1993:A32-A100, (770) 488-7160.

- The data collected and the timeframe for followup of live births be consistent with the research question(s) of interest. For example, in studies where the effects on the fetus or infant require some time to manifest an extended followup is appropriate. congenital anomalies and other complex abnormalities be reviewed and classified by a specialist in the field. For example, not all limb defects are the same; certain combinations of defects may constitute a syndrome or have a common etiology recognizable only by a specialist. Misclassification or inappropriate grouping of outcomes may lead to erroneous conclusions.
- If using an internal comparison group, the method of assessment and type of personnel responsible for assessment of infants be identical for both the exposed and comparison groups. Blinding of assessors to exposure would also decrease the probability of bias.

9. Sample sizes for registries

Determination of an adequate sample size depends on the objective and design of the registry. Consideration should be given to the anticipated frequency of product exposure in pregnant women that will influence the ability for timely enrollment of pregnant women and the baseline incidence of pregnancy outcomes and congenital anomalies or other abnormalities of interest.

We recommend that sample sizes be sufficient to show either "no" difference based on an acceptable limit for the confidence interval of the difference between the exposed and comparison group, or alternatively, to detect a clinically significant difference (e.g., an x-fold increase in the outcome of concern).

In the protocol and when reporting results from pregnancy exposure registries, the statistical power of the registry to rule out or detect a difference based on the anticipated or existing sample size should be specified.

To calculate sample sizes for a pregnancy exposure registry, five variables need to be specified (Strom 2000):

- a **or Type I error** (the probability of concluding there is a difference when one does not exist) and whether one-tailed or two-tailed. Conventionally, α is usually set at 0.05 although this need not be the case. The smaller the α, the larger the required sample size.
- b **or Type II error** (the probability of missing a real difference). β is usually set at 0.1 or 0.2 although this need not be the case. The smaller the β, the larger the required sample size.
- **minimum relative risk** to be detected. The smaller the relative risk to be detected or ruled out, the larger the required sample size.
- **background incidence** of abnormality of interest in unexposed group. The rarer the outcome of interest, the larger the required sample size.

- **ratio of unexposed to exposed subjects**. If using an internal comparison group, increasing the number of unexposed pregnancies per exposed pregnancy (up to a maximum of 4) can reduce the number of exposed pregnancies required and increase the statistical power.

Several different formulas can be used to calculate the required sample size based on these variables (e.g., Gail 1974, Strom 2000). We recommend consulting a statistician to determine which method should be used based on the specific requirements of the registry.

When estimating the number of exposed pregnancies to be enrolled prospectively, it is important to be aware that approximately 62 percent of clinically recognized pregnancies will result in a live birth, 22 percent will end in elective termination, and 16 percent will result in fetal loss (i.e., spontaneous abortions and fetal death/stillbirth) (Ventura et al., 2000). These population estimates vary considerably by maternal age and health. In addition, the rates are based on the general population and may not apply to specific disease groups (e.g., epilepsy, diabetes). If the fetal effect of concern occurs only in live born infants, it is important to estimate the number of expected live births within pregnancies enrolled prospectively early in gestation, considering the expected incidence of elective terminations and spontaneous abortions, fetal deaths, and stillbirths.

Overall, major congenital anomalies (i.e., those incompatible with life or requiring medical/surgical intervention) occur in approximately 4 percent of live born infants with individual major anomalies occurring much less frequently (March of Dimes 2001). Minor anomalies may be 10 to 20 times more common than major ones (Leippig et al., 1987) and 20 percent of infants with one or more minor congenital anomalies also have a major birth defect (Leippig et al., 1987).

The March of Dimes (2001) reports the following rates for various pregnancy outcomes and fetal abnormalities:

- Spontaneous abortions/miscarriage (loss prior to 20 weeks): 1/7 known pregnancies
- Low birth weight (<2500 grams): 1/12 live births
- Fetal death/stillbirth (loss after 20 weeks): 1/200 known pregnancies
- Any major birth defect: 1/25 live births
- Heart and circulation defects: 1/115 live births
- Genital and urinary tract defects: 1/135 live births
- Nervous system and eye defects: 1/235 live births
- Club foot: 1/735 live births
- Cleft lip with or without cleft palate: 1/930 live births

10. Data presentation and analysis

Descriptive statistics are the primary approach for summarizing data from a pregnancy exposure registry. However, given the heterogeneous nature of data obtained in pregnancy exposure registries, there is no one 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.

We recommend that:

- Data collected prospectively be analyzed separately from any collected retrospectively. All reports within each category should be stratified by pregnancy outcome (spontaneous abortion, elective termination, fetal death/stillbirth, live birth) and timing of exposure. Further stratification will depend on the amount of data available. Retrospective reports will not provide an accurate risk calculation, but can provide important qualitative data. For instance, infants born with a specific constellation of anomalies can be evaluated as a case series.
- When risk estimates are calculated, only outcomes from prospectively collected data be included. There are no published epidemiologic standards for calculating risk estimates or pregnancy outcomes using prospective data from a pregnancy exposure registry. However, although unvalidated, one publication offers some ideas on methods that could potentially be used (Goldstein et al., 2001).
- The 95 percent confidence intervals around the estimated rates of any fetal abnormalities as well as the 95 percent confidence intervals for estimates of the differences between exposed and comparison groups be presented.

If sample size allows, other analytic approaches can be considered. These analyses include life table analyses and multivariate analyses that adjust for covariates. For multidrug registries, a within-registry comparator or nested case-control analysis may be possible.

11. Use of an independent data monitoring committee

To ensure scientific integrity and appropriate patient protection, we encourage each registry to have an independent data monitoring committee similar to those used for clinical studies.[7] Members of the committee could include experts in obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, and any relevant therapeutic areas. The committee could advise and participate in establishing and operating the registry. The committee could also assist in the review of data, classification of any birth defects and the dissemination of information to ensure that results are interpreted and reported accurately. We recommend that the role and duties of the committee be specified in the protocol.

12. Multidrug pregnancy exposure registries

[7] A draft *Guidance for Clinical Trial Sponsors on the Establishment and Operataion of Clinical Trial Data Monitoring Committees* was issued on November 11, 2001. When finalized, it will represent the Agency's thinking on this issue.

A multidrug pregnancy exposure registry actively collects information on exposure to various drug therapies in specific diseases, such as human immunodeficiency virus (HIV) (White et al., 1997), epilepsy (The North American Pregnancy and Epilepsy Registry 1998), or asthma (Lipkowitz 1999; Scialli 1999). In some cases, a general multidrug registry, such as that conducted by a teratogen information service, collects information on drugs for unrelated indications. Multidrug registries have advantages over single drug registries with respect to efficiency and economy. They also have the advantage of having comparison groups of pregnant women unexposed to the medical product of interest readily available.

To help avoid redundancy and to prevent overburdening patients, physicians, and scientific experts with multiple requests to participate in individual studies, we encourage companies to work together to develop multidrug registries. It has been suggested that rather than conduct a separate pregnancy exposure registry for new drugs, a centralized pregnancy exposure registry should be established for drugs of unknown human teratogenicity that are likely to be used by women of reproductive age (Honein et al., 1999).

VII. HOW CAN OTHER STUDIES HELP?

The main utility of a pregnancy exposure registry is to provide margins of reassurance about absence of risk or to signal suspicions of risk. They are the most feasible study design at the time of first marketing. However, other studies may be called for to confirm or clarify any signals obtained from a registry.

Case control studies are appropriate to evaluate rare adverse birth outcomes and identify whether the drug in question is an associated risk factor. Case control studies can also evaluate outcomes that would require long-term followup in a registry model. They can be efficiently designed and implemented, and even nested within an existing pregnancy exposure registry when there are questions about other risk factors or contributing exposure details.

Studies using automated databases (e.g., HMOs, Medicaid) linking maternal exposure to infant outcome can also provide drug exposure information during pregnancy (e.g., Drinkard et al., 2000, Cooper et al., 2002). This design allows for evaluation of both pregnancy and fetal outcomes. However, it may be very difficult to find enough pregnancy exposures in any automated system unless the product is widely used, particularly early in product marketing.

Other systems and methodologies used for pharmacoepidemiology studies have been described elsewhere (Strom 2000; Hartzema et al., 1999).

VIII. WHAT ARE THE REGULATORY REPORTING REQUIREMENTS?

The following information, based on current regulations and guidance, describes how to report pregnancy exposure registry information to the Agency.

A. Individual Case Reports

The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information.[8] Accordingly, a sponsor holding marketing authorization for an approved drug or licensed biological product must submit to the Agency, within 15 calendar days, reports of adverse events from the registry that are both *serious* and *unexpected* by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event (see 21 CFR 310.305(c)(1), 314.80(c)(2)(iii) and (e), and 600.80(c)(1), (c)(2)(iii) and (e)). Current reporting requirements in the regulations consider any congenital anomaly within the definition of a serious adverse event (21 CFR 314.80(a) and 600.80(a)).

Pregnancy exposure registries that are run independently of any sponsors holding marketing authorizations are not subject to postmarketing regulatory reporting requirements. However, investigators running such registries may forward reports of any serious adverse events including congenital anomalies to the sponsor of the medical product or report directly to the FDA MedWatch office (1-800-FDA-1088 or http://www.fda.gov/medwatch).

B. Status Reports

The sponsor of any pregnancy exposure registry required by FDA or conducted as part of a written postmarketing study commitment shall, as required under 21 CFR 314.81(b)(2)(vii), 314.98(c), 601.70, and 601.28, submit to the Agency an annual status report. Sponsors of pregnancy exposure registries not subject to 21 CFR 314.81(b)(2)(vii), 314.98(c), and 601.70 are invited to include a status report in the annual report or in the periodic safety report (21 CFR 314.80(c)(2), 314.98 and 600.80(c)(2)) as recommended by the International Conference on Harmonisation (ICH) for studies that address safety issues.[9]

We recommend that the status report describe the study design and summarize the status of the planned, initiated, in progress, or completed pregnancy exposure registry conducted by or otherwise obtained by the sponsor during the reporting period (see information to include below). Any publications based on data from the pregnancy exposure registry should be included. The status report should also provide a descriptive summary of progress to date, interpretation of findings and appropriate analyses with comments on the clinical significance of the findings. Copies of full reports may be appended, if appropriate.

Where relevant to the registry, we recommend the status report include the following, presented separately for prospective and retrospective reports:

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[8] See the guidance for industry *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

[9] See guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.*

1. Basic Information:

- number of pregnant women enrolled to date
- number of pregnancies with outcome known (stratified by live birth, spontaneous abortions, elective terminations, fetal deaths/stillbirths)
- number of pregnancies with outcome pending
- number of pregnancies lost to followup

2. For pregnancies with known outcome, line listings and summaries of:

- demographics, obstetrical, and medical history of mothers
- weeks of gestational age at exposure
- dose and duration of exposure
- weeks of gestational age at completion or termination of pregnancy
- for live births and deaths/stillbirths, whether multiple birth, small for gestational age, preterm delivery, and congenital anomalies or other fetal abnormalities
- for spontaneous abortions and elective terminations, abnormalities in products of conception

IX. WHEN SHOULD A REGISTRY BE DISCONTINUED?

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

- Sufficient information has accumulated to meet the scientific objectives of the registry (i.e., numeric targets or effect size)
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or loss to followup
- Other methods of gathering appropriate information become achievable or are deemed preferable

The criteria for termination of the study should be predetermined and specified in the protocol.

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ATTACHMENT A

Examples of the Use of Observational Data in Labeling

Zovirax (acyclovir)

> "There are no adequate and well-controlled studies in pregnant women. A prospective epidemiological registry of acyclovir use during pregnancy has collected data since June 1984. As of December 1997, outcomes of live births have been documented in 552 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that of the general population. However, the small size of the registry is insufficient to evaluate the risk for specific defects or to permit definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Meruvax II (rubella virus vaccine live)

> "In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: In a 10 year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain) none of the newborns had abnormalities compatible with congenital rubella syndrome."

Sandimmune (cyclosporine)

> "The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune (cyclosporine) on these pregnancies from the effects of the other immunosupppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation."

Septra (trimethoprim and sulfamethoxazole)

"While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursell[1] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter."

Pulmicort Turbohaler (budesonide)

"As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (approximately 1/3 the maximum recommended daily inhalation dose in adults on a mcg/m 2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m 2 basis). No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 mcg/kg/day (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m 2 basis). Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Studies of pregnant women, however, have not shown that PULMICORT TURBUHALER increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2,014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8 % vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively). These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%). Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, PULMICORT TURBUHALER should be used during pregnancy only if clearly needed."

[1] Brumfitt, W., R. Pursell, 1973, "Trimethoprim Sulfamethoxazole in the Treatment of Bacteriuria in Women, *J Infect Dis*., 128(suppl):S657-S663.

ATTACHMENT B

Data Elements to Consider When Designing a Pregnancy Exposure Registry

A. General

Patient identifier
Name of reporter at initial contact with the registry
Date of initial contact with the registry
Dates of any followup contacts
Telephone number of reporter
Additional contact names and phone numbers (if reporter is the patient)

B. Maternal Information

Source of information (e.g., obstetrician, pregnant woman, other)
Birth date
Race
Occupation
Maternal medical history (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other)
Obstetrical History:
- Number of pregnancies and outcome of each (live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy)
- Previous maternal pregnancy complications
- Previous fetal/neonatal abnormalities and type

Current Pregnancy:
- Date of last menstrual period
- Complications during pregnancy (including any adverse drug reactions) and dates
- Number of fetuses
- Labor/delivery complications
- Disease course(s) during pregnancy and any complications
- Medical product exposures (prescription drugs, OTC products & dietary supplements):
  - Name
  - Dosage & route
  - Date of first use & duration
  - Indication
- Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount

Family History (specify type, maternal/paternal, etc.):

Spontaneous Abortions
Anomalies/Malformations
Multiple fetuses/births

C. Neonatal 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
Gestational outcome (live born, fetal death/stillborn, spontaneous abortion, elective termination)
Sex
Pregnancy weight gain of mother
Obstetric complications (e.g., pre-eclampsia, premature labor, premature delivery)
Pregnancy order (singleton, twin, triplet)
Results of neonatal physical examination including
Anomalies diagnosed at birth or termination
Anomalies diagnosed after birth
Weight at birth indicating whether small, appropriate, or large for gestational age
Length at birth
Condition at birth (including when available Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
Neonatal illnesses, hospitalizations, drug therapies

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