

FDA Public Meeting: Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products during Pregnancy in the Post-Approval Setting

Background Summary

1. Introduction

At the time of Food and Drug Administration (FDA) approval of a new drug or biological product there are often limited data on the safety of the product when used during pregnancy. Thus, there is often an absence of evidenced-based information for healthcare providers to use when prescribing or counseling pregnant women.¹ Obtaining human pregnancy data to inform product labeling is important for drug and biological products and collection and analyses of safety data on their use during pregnancy is usually performed post-approval.

2. Pregnancy Registries

Drug manufacturers are required to report adverse events, including birth defects, to the FDA Adverse Event Reporting System (FAERS); however limitations of spontaneous reporting include underreporting, reporting biases, missing information on clinical details or important other exposures, and perhaps most importantly, a lack of a denominator of exposed pregnancies to calculate incidence rates of adverse outcomes. In 2002, in an effort to standardize industry's approach to post-market data collection in pregnant women, FDA published guidance to industry entitled, "Guidance for Industry on Establishing Pregnancy Exposure Registries."² Since the publication of the guidance, pregnancy registries have become a primary method for the Agency to request post-approval studies in pregnant women.

In this guidance, a pregnancy exposure registry is defined as a prospective, observational study that actively collects information on cases in which women are exposed to a medical product during pregnancy and the subsequent pregnancy outcomes. Importantly, this study type allows for data on drug exposure during pregnancy to be collected before pregnancy outcomes are known. Pregnancy registries are generally designed to include elements such as outcome definitions, internal and/or external comparator group(s), data collection methods, and a statistical method.³ However, in order to collect statistically meaningful data, the sample size of a pregnancy exposure registry should be large enough to show either no difference based on an acceptable limit for the confidence interval of the difference between the exposed and comparator group, or alternatively, to detect a clinically significant difference (e.g., an x-fold

¹ Goldkind S, Sahin L, Gallauresi B. Enrolling pregnant women in research Perspective. NEJM 2010; 362:2241-2243.

² Kennedy DL, Uhl K, Kweder S. Pregnancy Exposure Registries. Drug Safety 2004; 27(4): 215-228.

³ FDA Guidance for Industry: Establishing Pregnancy Exposure Registries. August 2002.

increase in the outcome of concern). Generally, a pregnancy registry should be designed to include appropriate assessment and follow up of outcomes, and measures to ensure quality of data collection and review.⁴ Drugs or biological products that should be studied using pregnancy exposure registries include those that have a high likelihood of use or inadvertent exposure by females of reproductive potential and pregnant women.⁵

In a recent publication by the Agency for Healthcare Research and Quality (AHRQ), advantages of pregnancy registries included the prospective design, the ability to collect detailed patient level information such as the timing of exposure and dose, and covariate data, which can reduce recall bias, exposure misclassification, and confounding.⁶

3. Challenges with Pregnancy Registries

FDA has had a growing concern that pregnancy registries often fail to provide clinically meaningful information because of inadequate enrollment. Enrollment in registries may be low because of inadequate recruitment efforts and/or lack of incentives for patients to enroll. For example, healthcare providers may not have sufficient time to spend time with patients discussing the registry, enroll patients, and complete case report forms or send medical records. Additionally, enrollment may be low because of low use of the product in pregnant women. Other challenges that FDA has encountered in reviewing pregnancy registry study reports include, but are not limited to, the lack of standardization of data collection, inconsistencies in outcome definitions/inclusion/exclusion criteria, and variations in use of a comparison population.

The European Medicines Agency (EMA) recently conducted an analysis of pregnancy exposure research and has noted similar issues in obtaining quality pregnancy exposure data.⁷ The EMA review included strengths and limitations similar to those mentioned above. The report also raised the issues of potential selection bias, due to the voluntary nature of patient enrollment, and

⁴ Howard TB, Tassinari MS, Feibus KB, Mathis LL. 2011. Monitoring for teratogenic signals: Pregnancy registries and surveillance methods. *Am J Med Genet Part C Semin Med Genet* 157:209–214.

⁵ Definition of “Females of reproductive potential”: Girls who have entered puberty (girls who are at least Tanner Stage 3 and have not yet had a menses) and all women who have a uterus and ovaries and have not passed through menopause.

⁶ Gliklich R, Dreyer N, Leavy M, eds. *Registries for Evaluating Patient Outcomes: A User’s Guide*. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. <http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm>. Vol 2, page 155.

⁷ Charlton R and de Vries C. *Systematic Overview of Data Sources for Drug Safety in Pregnancy Research*; Consultancy EMA/2010/29/CN; European Medicines Agency; June 2012; Available at:http://www.encepp.eu/structure/documents/Data_sources_for_medicines_in_pregnancy_research.pdf

loss to follow-up. Often there is limited ability to draw clear conclusions due to low frequency of the exposure and outcome of interest.

4. Alternatives to Pregnancy Registry studies

Recently, there has been an emergence of alternatives to pregnancy registry studies for the collection of safety data for products used during pregnancy, such as studies using linked mother-baby databases and pharmacovigilance approaches, as well as combined pregnancy registry-case control studies.

An example of a linked mother-baby database is the FDA funded Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), which links health information on mothers and their infants derived from multiple healthcare systems, including managed care, integrated health systems, and Medicaid databases.⁸ Other examples of linked mother-baby databases include the Department of Defense databases and the Vaccine Safety Datalink, which is a collaborative effort between the Centers for Disease Control and Prevention (CDC)'s Immunization Safety Office and several managed care organizations.^{9,10,11} The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) uses a combined prospective cohort and case control approach to assess pregnancy outcomes.¹² Pharmaceutical companies sometimes use global pharmacovigilance with enhanced methods for data collection in pregnant women.¹³

The EMA has also conducted a comprehensive search of published literature and found numerous alternative data sources being used for pregnancy-related research questions. The EMA grouped alternative data sources into the following three broad categories: 1) population-based surveillance registers that rely on linked data sets (e.g., Scandinavian national birth

⁸ Andrade SE, Davis RL, Cheetham TC, Cooper WO, Li DK, Amini T, Beaton SJ, Dublin S, Hammad TA, Pawloski PA, Raebel MA, Smith DH, Staffa JA, Toh S, Dashevsky I, Haffner K, Lane K, Platt R, Scott PE. Medication Exposure in Pregnancy Risk Evaluation Program. *Matern Child Health J.* 2012 Oct; 16(7):1349-54.

⁹ Conlin AM, Bukowinski AT, Sevick CJ, DeScisciolo C, Crum-Cianflone NF. Safety of the pandemic H1N1 influenza vaccine among pregnant U.S. military women and their newborns. *Obstet Gynecol.* 2013 Mar; 121(3):511-8.

¹⁰ Robb MA, Racoosin JA, Worrall C, Chapman S, Coster T, Cunningham FE. Active surveillance of postmarket medical product safety in the Federal Partners' Collaboration. *Med Care.* 2012 Nov; 50(11):948-53.

¹¹ Naleway AL, Irving SA, Henninger ML, Li DK, Shifflett P, Ball S, Williams JL, Cragan J, Gee J, Thompson MG; for the Vaccine Safety Datalink and Pregnancy and Influenza Project. Safety of influenza vaccination during pregnancy: A review of subsequent maternal obstetric events and findings from two recent cohort studies. *Vaccine.* 2014 Apr 14 [Epub ahead of print].

¹² Louik C, Ahrens K, Kerr S, Pyo J, Chambers C, Jones KL, Schatz M, Mitchell AA. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. *Vaccine.* 2013 Oct 17; 31(44):5033-40.

¹³ Khromava A, Cohen CJ, Mazur M, Kanesa-thasan N, Crucitti A, Seifert H. Manufacturers' postmarketing safety surveillance of influenza vaccine exposure in pregnancy. *Am J Obstet Gynecol.* 2012 Sep; 207(3 Suppl):S52-6.

registers that are linked to prescription data), 2) healthcare databases (e.g., claims and electronic medical record databases), and 3) purpose-built data sources such as case-control surveillance systems (e.g., the CDC's National Birth Defects Prevention Study).⁷

5. FDA Exploratory Review of Pregnancy Registries

In preparation for this public meeting, FDA undertook an exploratory review of selected pregnancy registries to assess the current status of these post-approval studies and their ability to collect data to inform product labeling. Pregnancy registries for review were selected from the products listed on the FDA Office of Women's Health (OWH) webpage.¹⁴ The webpage includes pregnancy registries that were developed in response to post-marketing commitments (PMCs) or requirements (PMRs) and pregnancy registries that were not regulatory obligations. The results of this exploratory review will be presented at the public meeting.

6. Objectives of public meeting

The objective of this public meeting is to engage researchers, industry, public health agencies, health care providers, and the public through presentations and panel discussions on the following topics:

- Current status of pregnancy registries and challenges in gathering data regarding drug and biological products used during pregnancy
- Strategies to improve the design and conduct of pregnancy registries
- Alternative approaches for data collection, such as
 - pharmacovigilance methods
 - claims-based studies
 - combined prospective cohort and case control studies
 - studies using large linked healthcare databases and
 - other methodologies
- Best practices for communicating information to health care providers and patients about existence of and the need to enroll women into pregnancy registries to collect safety data.

Information obtained from this meeting will be used to update and revise the guidance on the design and conduct of pregnancy registries, as well as to identify alternative study designs that may be used to help characterize safety of drugs and biological products in pregnancy.

¹⁴ FDA Office of Women's Health. Women's Health Research - Pregnancy Registries. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm>.

Questions for the panel

Topic 1: Pregnancy Registries: Perspectives/ challenges relating to data collection and analyses

1. Discuss pregnancy registries as a method for collecting data on ascertaining the risks associated with *in utero* exposure to drugs and biological products. What are the advantages and greatest challenges in the design, data collection and analyses of a prospective, observational pregnancy registry?
2. What steps can be taken to overcome the challenges discussed in question 1? In your response please consider the following: methods to improve data collection and quality, need for more consistent outcome definitions, options for comparator groups, designs to help achieve adequate sample size, etc.
3. What are the criteria for determining whether a single product or a multi-product/disease-based prospective, observational pregnancy registry design is appropriate? What are the challenges and advantages of developing and conducting a multi-product registry?

Topic 2: Enrollment, Retention and Communication

1. How can enrollment and retention in pregnancy registries be improved? Consider in your comments, overcoming barriers to enrollment, use of enrollment and study participation incentives, and minimizing loss to follow up.
2. How can overall awareness of pregnancy registries as well as the existence of available registries be increased for patients and healthcare providers?
3. Discuss the role of the FDA in communicating information about pregnancy registries. Consider in your comments, recommendations for the current FDA Office of Women's Health webpage and other methods FDA could use to communicate the existence of a pregnancy registry.

Topic 3: Alternative approaches for data collection

1. Discuss alternative study designs and methods including population-based data systems for the collection and analyses of postmarketing safety data for drugs and biological products used during pregnancy. Consider how alternative approaches can help address some of the challenges/limitations of pregnancy registries and the advantages/disadvantages of these alternative approaches.

2. Discuss how these alternative approaches might be developed into comprehensive population-based models or systems that can be used more broadly by industry, regulators and researchers to address questions about outcomes relating to drug exposures in pregnancy. What type of governance model might allow for optimal maintenance and growth of these systems (e.g. MEPREP), as well as appropriate linkages to other relevant data?
3. Are there additional models/systems beyond those discussed here that should be explored?