

Sizing up the Pregnancy and Lactation Labeling Rule: Understanding Challenges and Opportunities

As a strategic thought leader, Wolters Kluwer Clinical Drug Information partners with content experts to bring you the latest information on important changes in the healthcare space.

This white paper is based on a presentation by Drs. Michael Schatz, Christina Chambers, and Allen A. Mitchell, three stakeholders in the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) initiative. Dr. Schatz is an allergist at Kaiser-Permanente Medical Center in San Diego. Dr. Chambers is a professor of pediatrics and family medicine/public health and director of the OTIS Research Center at the University of California San Diego. Dr. Mitchell is a professor of epidemiology and pediatrics and director of the Slone Epidemiology Center at Boston University.

The labeling rules governing how medication risks associated with pregnancy and lactation are displayed on product packaging and inserts have been under scrutiny for years. In response to growing concerns among healthcare professionals about the utility of the pregnancy labeling format, the U.S. Food and Drug Administration (FDA) implemented new rules to improve pregnancy safety labeling.

The Pregnancy and Lactation Labeling Rule (PLLR) was issued in December, 2014, went into effect in June of 2015, and serves as an amendment to the Physician Labeling Rule (PLR) of 2006, expanding and revising the original stipulations to help providers get additional, more useful information that can help them more accurately and effectively assess risks and benefits of using medications and vaccines during pregnancy.ⁱ A 2011 study reports that in the United States, approximately 90% of women took at least one medication during pregnancy, and 70% took at least one prescription medication.ⁱⁱ

Use of medications during pregnancy has historically been one of the least-developed areas of clinical pharmacology and drug research, because few medications have specifically been tested for safety and

efficacy during pregnancy.ⁱⁱⁱ As a result, pregnant women may not receive medically important therapies or may be exposed to potential risks from medications where risk evidence is lacking.^{iv} At the same time, medication use by women who are pregnant or breastfeeding is on the rise. Consider that first trimester medication use has increased by more than 60% over the past 30 years, and use of four or more medications during the same timeframe has nearly tripled.^v

The PLLR is a culmination of efforts to address criticisms regarding the relative dearth of pregnancy and lactation information presented on labels, as compared to information about use among the general population, and confusion from healthcare providers over how that information was formatted.^{vi} New guidelines replace the traditional system of categorizing risk via letters A, B, C, D and X, opting instead for more in-depth data on potential risks, clinical considerations, and dosing via three subsections: Pregnancy, Lactation, and Females and Males of Reproductive Potential. The changes are intended to address the simplistic representations of the previous system, which could have been incorrectly interpreted as a grading system, according to the FDA.^{vii}

While many in industry and clinical practice applaud this new effort to provide more content-rich, relevant information regarding safe and effective use of medications during pregnancy, it is also well-understood in the medical community that the new guidelines do not address the greater issue of the very limited relevant evidence available regarding risk or safety of most medications and vaccines. Because clinical trials for new drugs are not typically conducted with pregnant women, information must be aggregated from observational resources. The unfortunate reality is that very limited human pregnancy safety data exist for the vast majority of drugs currently on the market.^{viii}

**LABELING RULE:
A HISTORIC PERSPECTIVE**

The first regulations governing drug labeling for pregnancy and lactation were issued by the FDA in 1979. Designed in the format of the lettering system in use until June 2015, the categories A, B, C, D, and X were generally defined according to Figure 1.

As the FDA identified issues associated with use of this system in clinical practice, work toward the Pregnancy and Lactation Labeling Rule revision was initiated in 1994 following a position paper published by the Public Affairs Committee of the Teratology Society. A Part 15 public hearing was held by the FDA, and the proposed rules were written with new labeling guidelines based on expert input. Between 2008 and 2013, the draft rules were issued and revised after public comment, and the PLLR was later published in December 2014.

Based on recent study data, the PLLR will likely be relevant to more than 6 million pregnancies that occur in the U.S. each year and will be implemented via a staggered timeline over the next 3-5 years due to the massive nature of the undertaking. The implementation is expected to be complete by June 30, 2020.

Problems identified with the previous letter classification system stemmed primarily from ongoing confusion over how to interpret the letters and concerns that the information provided lacked depth. Because the risk categories were represented as A, B, C, D, and X,

providers and patients were naturally inclined to associate them with letter grades that might be used in a school system. For instance, the letter B within this classification framework would suggest greater safety than a C or D.

In contrast, the categories were not set up to represent a definitive scaled approach to risk. The B category might be assigned based on the fact that animal reproduction studies failed to demonstrate risk, while human studies may have only found no evidence of risk in the first trimester or may not have been done at all. From another vantage point, the C category might have been used to suggest the absence of studies in general, or alternatively, it may have pointed to an animal reproduction study that revealed a potential adverse effect on the fetus when no human studies existed.

Adding to the confusion, category X was often interpreted as indicating a “problem” drug that should be avoided altogether. In reality, the definition of this category and the data presented did not always align with the assertion that a particular drug is known to lead to birth defects in humans.

PREGNANCY CATEGORIES

A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

FIGURE 1

In an effort to address these issues, the PLLR is designed to reduce confusion and help healthcare providers make better choices when selecting drugs by providing a more extensive analysis of risks and benefits.

PLLR: UNDERSTANDING THE SCOPE OF CHANGES

The PLLR covers all prescription drugs approved on or after June 30, 2001, and it requires that manufacturers revise the content and format of the Pregnancy and Nursing Mothers subsections of labeling. Under these guidelines, prescription drugs are required to remove letter categories and replace them with an Integrated Risk Summary.^{ix} While drugs approved before the June 30, 2001, cutoff are not required to reformat their labeling, they are required to remove the letter categories.

The prior subsections that included 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers are now revised to 8.1 Pregnancy (including labor and delivery), 8.2 Lactation (including nursing mothers), and 8.3 Females and Males of Reproductive Potential (Figure 2). The information now included in the newly-created 8.3 subsection includes risk data that were formerly scattered across several previous subsections of the label and not clearly defined, for example, as applicable to the topic of potential effects of drug exposure on fertility.

Through this revised format, the goal is to more clearly define risk as it pertains to each subsection. Beginning with 8.1 covering pregnancy, PLLR labeling requirements call for:

- Information regarding pregnancy exposure registries (if they exist) for particular drugs and contact information for those registries
- A risk summary that details information available from human, animal, and pharmacology studies

- Clinical considerations as to whether medical or disease factors should be considered in the context of treatment in pregnancy
- Actual data from research that supports the risk summary and clinical considerations

Inclusion of background risk information and supporting evidence is new to labeling. The new risk summary is formatted to lead with human research data related to risk, followed by animal data and pharmacology information when available. For example, pharmacology information may speak to the mechanism of action of the drug and then include background risk information on adverse pregnancy outcomes in the general population and in individuals with the condition the drug is used to treat. In the case of a drug that is not systemically absorbed, the risk assessment need only contain a statement that the drug is not absorbed systemically and is not expected to result in fetal exposure.

The clinical considerations section provides further information relevant to prescribing and risk benefit counseling under the sub-sections Maternal Adverse Reactions, Fetal/Neonatal Adverse Reactions, and Labor and Delivery. An example of information presented in this section could include a statement about increased risk of

preeclampsia, premature birth, and low birth weight in women with poorly- or moderately-controlled asthma.

The final section devoted to data provides a description of the scientific basis of the risk summary and clinical considerations. Information provided includes the type of study, number of subjects, study duration, exposure information, and limitations of the data.

With the exception of pregnancy registry information, the new 8.2 Lactation subheading replaces the previous Nursing Mothers section and includes information requirements similar to 8.1. It includes subheadings for a risk summary, clinical considerations and data, and risk information for systemically-absorbed drugs. The effect of the drug in human milk is presented first, followed by effects of the drug on the breastfed child, and effects of the drug on milk production. The section concludes with a risk and benefit statement.

Within the third subheading, titled Females and Males of Reproductive Potential, requirements and recommendations are included for pregnancy testing and contraception when human or animal data suggest drug effects on fertility. Information is provided under three headings including Pregnancy Testing, Contraception, and Infertility.

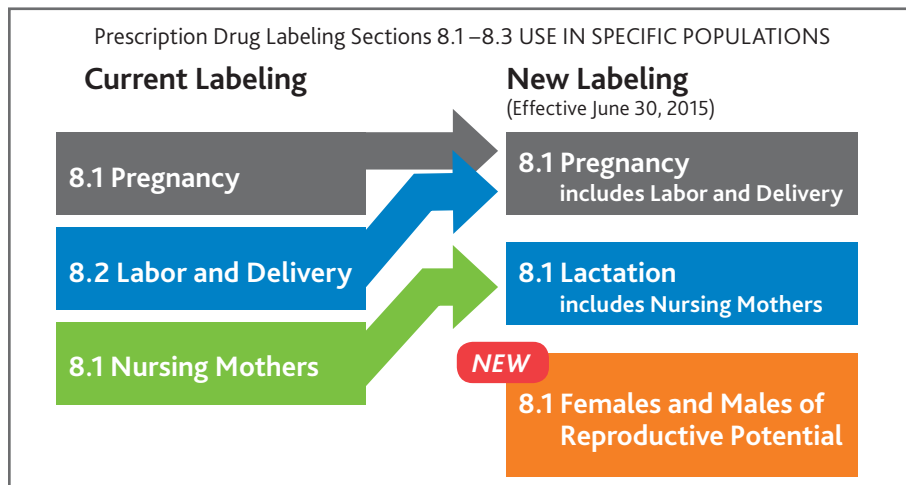


FIGURE 2

THE NEED FOR BETTER DATA

While new labeling requirements are a critical step toward improving the safe use of medications and vaccines for pregnant and lactating women, the greater issue rests with a lack of human data relevant to these areas. When research data are available, they often have substantial limitations.

For instance, traditional pregnancy registries are often characterized by small sample sizes and lack of comparison groups that encompass women from the same study population who have not used the drug under review. In essence, comparisons are made against the general population, making it difficult to address differences between those who have taken a medication and those who have not.

While some larger cohort studies can provide some information relevant to pregnancy, they often come from countries outside the U.S. where fewer exposures to a drug of interest may exist. Administrative or claims databases could be a good source of information, but once again, there is often limited exposure to the drug of interest and there is difficulty in these types of studies in controlling for confounding variables. For example, these types of data sources do not frequently assess whether a mother has taken folic acid supplements or consumed alcohol or tobacco, making it difficult to make meaningful comparisons.

In an effort to provide better quality information that clinicians can more confidently translate into clinical practice, the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) was introduced as a nationwide post-marketing surveillance system to monitor use and safety of vaccines

and medications during pregnancy. A collaborative effort between the American Academy of Allergy Asthma and Immunology, the Organization of Teratology Information Specialists (OTIS) Research Center at the University of California San Diego, and the Slone Epidemiology Center at Boston University, the initiative aims to speed identification of harmful drugs and provide more extensive reassuring data for those drugs and immunizations that are considered safe during pregnancy.^x

Through a coordinated effort involving both prospective registry surveillance and case-control surveillance, VAMPSS builds a solid, credible foundation by gathering information directly from the patient. This format maximizes ascertainment of confounder information that might not be readily available through a patient medical record — a primary limitation of current pregnancy and lactation research data.

Case control surveillance focuses on birth defects — specific congenital malformations which occur in numbers too few to allow meaningful risk identification in any existing pregnancy registry. It also captures the

prevalence of drug and vaccine use. The prospective registry surveillance arm entails enrollment and follow-up of pregnant women who are exposed to vaccines or taking medications during pregnancy, a concurrently enrolled comparison group of unexposed women, and ability to evaluate the range of pregnancy outcomes including birth defects, spontaneous abortion, preterm delivery, pre- and postnatal growth, and pregnancy complications.

In essence, VAMPSS was developed specifically to provide the type of comprehensive information regarding the risks and safety of vaccines and medicines during pregnancy that patients and providers need. VAMPSS data should provide valuable information for the new pregnancy label and all potential stakeholders.

CONCLUSION

Improvements to pregnancy labeling rules have come a long way over the past decade. As the industry advances safer practices, the next step is ensuring that data provided through the new labeling is more comprehensive and credible.

-
- i <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>
 - ii "Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008." Mitchell AA, et al; National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2011 Jul; 205(1):51.e1-8. doi: 10.1016/j.ajog.2011.02.029. Epub 2011 Apr 22.
 - iii <http://www.ncbi.nlm.nih.gov/pubmed/19104374>
 - iv Id.
 - v "Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008." Mitchell AA, et al; National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2011 Jul; 205(1):51.e1-8. doi: 10.1016/j.ajog.2011.02.029. Epub 2011 Apr 22.
 - vi <http://www.uspharmacist.com/content/d/feature/i/3034/c/51060/>
 - vii <http://www.foxnews.com/health/2014/12/04/fda-changes-labeling-for-drugs-used-during-pregnancy-lactation/>
 - viii <http://www.cdc.gov/pregnancy/meds/treatingfortwo/data.html>
 - ix <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>
 - x <http://www.aaaai.org/about-the-aaaai/strategic-relationships/vampss/vampss-consumer.aspx>

