

[The Food and Drug Administration's Pregnancy and Lactation Labeling Rule \(2014\)](#) ^[1]

By: Meek, Caroline Keywords: [drug label](#) ^[2] [drug law](#) ^[3] [Pregnancy and Lactation Labeling Rule](#) ^[4] [Pregnancy](#) ^[5] [drug safety](#) ^[6]

In 2014, the United States [Food and Drug Administration](#) ^[7] published the Pregnancy and Lactation Labeling Rule to amend previous guidelines for the prescription of drugs for pregnant and lactating women. The 2014 Pregnancy and Lactation Labeling Rule was intended to increase the safety and efficacy of prescription drugs by making drug labels easier for physicians to understand and utilize. The Pregnancy and Lactation Labeling Rule restructured drug labels and required that they include narratives describing drug-associated risks to women and fetuses, rather than using complicated letter categories. The Pregnancy and Lactation Labeling Rule changed the framework for drug labeling, making it easier for doctors to prescribe safe and effective drugs to pregnant women, lactating women, and people of reproductive capacity.

In the US, the FDA ensures the safety and efficacy of drugs by regulating drug manufacturers. In the first step of this process, the FDA proposes a possible rule and makes the draft rule available for public comment. Next, the FDA reviews and incorporates those comments. Finally, they publish the revised rule, which has the force and effect of law. Drug manufacturers and other entities within the FDA's jurisdiction must follow the rule set by the FDA. One kind of rule the FDA can set involves drug labeling. Drug labels contain information that is meant to guide how physicians and pharmacists prescribe drugs and how patients use drugs. The Pregnancy and Lactation Labeling Rule regulates the labels on drug containers, the handouts that come with prescription drugs, as well as the information that physicians use to prescribe those drugs.

For much of the twentieth century, drug labels did not include any information about the effects drugs might cause on pregnant women and their fetuses. The FDA began regulating drugs specifically used during [pregnancy](#) ^[8] in 1979 following several incidents where drugs caused negative effects in pregnant women and their fetuses. One incident involved thalidomide, a drug developed in Germany in the 1950s that doctors prescribed as a sedative and to reduce nausea in pregnant women. Thalidomide was advertised as safe for pregnant women. However, the drug caused limb deformities in children born to mothers who took the drug during [pregnancy](#) ^[8]. Another incident involved diethylstilbestrol, or DES, a drug marketed to pregnant women in the 1970s to prevent early labor. Researchers later found that DES caused cancer, and many female children born to mothers who took DES had a higher risk of developing a vaginal tumor called a clear carcinoma. That drug was discontinued in 1971. The FDA passed their first rule regulating the format and content of prescription drug labels in 1979. The 1979 rule established a five-category system in which letters were used indicate increasing risk a drug posed to the pregnant woman or [fetus](#) ^[9], with A indicating low risk and X indicating high risk. According to historians, the 1979 rule had several problems. First, the information pertaining to pregnant women was difficult to find. Second, the label did not include sufficient information to guide doctors' prescription of drugs.

The 1979 rule was amended in 2006 when the FDA issued the Physician Labeling Rule. Starting in 2006, the FDA eliminated the [pregnancy](#) ^[8] information in the "Precautions" section on labels and moved it to three new specific populations sections titled "Pregnancy," "Labor and Delivery," and "Nursing Mothers." The 2006 Physician Labeling Rule continued to use the letter categories to indicate the drug-associated risks posed to mother and [fetus](#) ^[9]. The new rule made that information easier to find.

The [pregnancy](#) ^[8] categories established in 1979 and maintained in 2006 were criticized by several groups. According to the Pediatric Advisory Committee within the FDA, the labels established by the 1979 Rule and maintained in the Physician Labeling Rule were overly simplistic and could lead to physicians or patients misinterpreting information. The Teratology Society, a scientific society focused on [birth defects](#) ^[10], did not support the use of standardized categories and asserted that the categories would not give people an accurate understanding of the risks associated with certain drugs. The [American College of Obstetricians](#) ^[11] and Gynecologists, or ACOG, indicated that the [pregnancy](#) ^[8] categories were confusing and unhelpful for patients and physicians. ACOG also requested that the FDA replace [pregnancy](#) ^[8] categories with written sections.

In 2014, the FDA issued the Pregnancy and Lactation Labeling Rule, which discontinued the letter categories in the "Pregnancy" section and replaced them with narrative descriptions of risk. The FDA first drafted the Pregnancy and Lactation Labeling Rule in 2008 and published it in 2014. The 2014 Pregnancy and Lactation Labeling Rule restructured the content of the 2006 Rule and introduced three headings, "Pregnancy," "Lactation," and "Females and Males of Reproductive Capacity." Within each of those headings, the Pregnancy and Lactation Labeling Rule specifically outlines what manufacturers must include on drug labels. The "Pregnancy" section includes the requirements for labels of drugs that women might use during [pregnancy](#) ^[8]. The "Lactation" section includes the requirements for labels of drugs that women might use while breastfeeding. The "Females and Males of Reproductive Capacity" section includes the requirements for labels of drugs that might impact fertility.

The first section in the Pregnancy and Lactation Labeling Rule is "Pregnancy." The [regulation](#) ^[12] separates the topics in the "Pregnancy" section to include information about a reaction reporting registry, summary of the risks, and guidance for physicians prescribing the drug. In 1999, The FDA created a system for collecting data about pregnant women's exposure to different medications. The FDA website hosts the Pregnancy Exposure Registry, which is separated into groups by type of medication the

pregnant women used. For example, there is a registry for pregnant women who have taken medication for seizures. The 2014 Pregnancy and Lactation Labeling Rule requires the first section on a drug label to include information about how a pregnant woman may participate in the registry. The next topic in the “Pregnancy” section is a risk summary. The risk summary section of the Pregnancy and Lactation Labeling Rule requires the second heading on the drug label to be summary of what happens to a fetus^[9] when the pregnant woman takes the drug during pregnancy^[8]. In that section, the FDA includes information pertaining to instances of limb deformities, death rate, and behavioral and functional impairment. When the information about drug-associated risk includes data from both human and animal studies, the FDA requires that the information derived from human studies comes before the information derived from animal studies. The last topic in the “Pregnancy” section is guidance for physicians prescribing the drug. The FDA requires that a drug label has a statement which specifies whether the drug poses serious risk to the pregnant woman or fetus^[9] and contains recommendations for changing the dosage of the drug during pregnancy^[8] and postpartum. That section must also provide information regarding the risk posed to the pregnant woman or fetus^[9] by the mother having the disease the drug is intended to treat. For example, a pregnant woman with high blood pressure might have increased fetal risk because of her high blood pressure, then the label of her blood pressure medication must state that the fetus^[9] is at risk.

After the “Pregnancy” section, the FDA outlines the requirements for drugs used by women during the period of breastfeeding in a section entitled “Lactation.” The “Lactation” section is similar to the “Pregnancy” section in structure. The FDA requires the first topic on a label to be a brief summary of risk. The FDA also requires that the human studies which support their conclusions about risk come before the animal studies. The FDA requires the second topic on a drug label to be about how the drug is absorbed in breastfeeding women. The Pregnancy and Lactation Labeling Rule separates drugs taken by breastfeeding women into two categories, drugs absorbed into the bloodstream and drugs not absorbed into the bloodstream. Drugs absorbed into the bloodstream of a breastfeeding woman can transfer to the infant and pose a health risk. The FDA requires last topic on a drug label to be guidance for physicians prescribing the drug. Specifically, the FDA requires that a label includes recommendations to ensure that an breastfeeding infant is not exposed to high concentrations of dangerous drugs. For example, the FDA requires the label of a drug that is dangerous in high concentrations in an infant to have a statement which states that physicians should only prescribe the drug infrequently or in small doses to minimize the infants’ exposure.

The final section in the Pregnancy and Lactation Labeling Rule is titled “Females and Males of Reproductive Potential.” Some drugs affect fertility or cause birth defects^[10] when females or males take those drugs during conception^[13]. The FDA established a section in the Pregnancy and Lactation Labeling Rule for women and men capable of reproducing. Historically, the FDA published information pertaining to contraception^[14] and pregnancy^[8] testing in “Warnings” and “Precautions” sections elsewhere on a drug label. Under the Pregnancy and Lactation Labeling Rule, that information is found in a third heading in the “Pregnancy” section, which outlines any information on pregnancy^[8] testing, contraception^[14], and infertility^[15]. The FDA says that having information about fertility, pregnancy^[8] testing, and contraception^[14] in several different sections on a drug label was confusing to physicians because the information was difficult to locate.

When the Pregnancy and Lactation Labeling Rule was announced in 2014, it was received positively by the scientific community. Sandra Kweder, director of the Office of New Drugs in the FDA Center for Drug Evaluation and Research, asserted that physicians interpreted the risk categories originally established in 1979 as a broad risk stratification system, although they were not meant to be a blanket decision making tool. Kweder stated that the FDA intended the Pregnancy and Lactation Labeling Rule to reflect the organization’s understanding that prescribing decisions during pregnancy^[8] are complex and require physicians to compare risks and benefits. According to George DeMaagd, professor of pharmacy, the changes established by the Pregnancy and Lactation Labeling Rule were useful. DeMaagd asserted that shifting from a risk category to a descriptive paragraph allowed women and physicians to have improved discussions about drug-associated risks. According to Miriam Dinatale, a member of the Pediatric Advisory Committee, the reorganization made drug labels clearer and thus improved physicians’ ability to counsel patients who take drugs. According to Marion Gruber, director of the FDA Office of Vaccines Research, implementation of the Pregnancy and Lactation Labeling Rule would require close collaboration between the FDA and drug manufacturers. Furthermore, Gruber asserted that the Pregnancy and Lactation Labeling Rule would require drug manufacturers, specifically vaccine manufacturers, to reconsider how they present risk to physicians and patients on drug labels.

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