Physician Labeling Rule (2006) [1]

By: Meek, Caroline Keywords: drug law [2] Physician Labeling Rule [3]

In 2006, the United States Food and Drug Administration [4], or FDA, published the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," also called the Physician Labeling Rule, to improve the safety and efficacy of prescription drugs and drug products. Within the Physician Labeling Rule, the FDA includes a section titled "Use in Specific Populations" or Section 8, which refers to drugs used by pregnant women, lactating women, and people of reproductive capacity. The FDA stated that the purpose of the Physician Labeling Rule was to make drug labels easier for physicians to understand and use when prescribing drugs to pregnant women. With the Physician Labeling Rule, the FDA improved patient-physician communication and the safety of drug use during pregnancy [5].

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 2006 Physician Labeling Rule specifically regulated labels on drug containers by establishing the kinds of information the labels must include.

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 [5] in 1979 following several incidents where drugs caused negative effects in pregnant women and their fetuses. One incident involved thalidomide, a drug developed in the 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 [5]. 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 included the requirement that manufacturers assign drugs to one of five pregnancy [5] categories. According to historians, the 1979 rule had several problems. First, the information regarding pregnant women was hard to find. Second, the label did not include sufficient information to guide doctors' prescription of drugs.

Before the 2006 Physician Labeling Rule, drug labels did not clearly indicate what effects drugs might have on pregnant and breastfeeding women and their infants. Instead, physicians and patients read about the effects of a drug taken in pregnancy [5] in a drug label section titled "Precautions." According to the Teratology Society, a scientific society focused on birth defects [6], the "Precautions" section was meant to separate pregnancy [5] guidance from non-pregnancy [5] guidance. The "Precautions" section also included information about how children or elderly people should use a drug. In 2006, the FDA changed the way drugs were labeled by restructuring the previous guidelines. The Physician Labeling Rule removed the pregnancy [5] information in the "Precautions" section of drug labels and moved it to three new specific populations sections called "Pregnancy," "Labor and Delivery," and "Nursing Mothers." The FDA asserted that the distinction made the information about drug risks and effects easier for people to find. Those new sections were located in a larger section called Section 8. According to the FDA's implementation guide, Section 8 was intended to improve the format, organization [7], and readability of drug labels.

Section 8 of the 2006 Physician Labeling Rule addresses specific groups of people. Section 8, also called the "Use in Specific Populations" section, contains three subsections regarding pregnant and lactating women. Those subsections are "Pregnancy," "Labor and Delivery," and "Nursing Mothers." In each section, drug manufacturers must explain on the label the risks inherent in taking the drug.

In the "Pregnancy" section, the FDA focuses on drugs used by women while they are pregnant, which they defined as conception [8] until the beginning of labor. That subsection states that a drug label must have a warning if the drug is already known to be absorbed into the bloodstream of the mother. Drugs absorbed into the bloodstream can transfer to a fetus [9] and can potentially pose a risk to pregnant women and developing fetuses. According to the FDA, those risks mean that those kinds of drugs require more extensive labeling under the 2006 Physician Labeling Rule.

If a drug transfers into a pregnant woman's bloodstream, potentially affecting the fetus [9], the 2006 Physician Labeling Rule requires that drug manufacturers classify the drug into one of five categories which include A, B, C, D, or X. Those categories imply increasing drug-associated risk to the mother or fetus [9], with A indicating low risk, and X indicating high risk. The Physician Labeling Rule states that a drug labeled as category A poses no risk to the fetus [9] in the first trimester [10]. When a drug has a category A label, it means that studies performed on pregnant human women did not demonstrate any risk for fetal abnormalities. Some abnormalities researchers look for when testing new drugs include changes in infant birth weight and limb formation. Category A drugs must also

be labeled with a statement that risk to the fetus [9] cannot be completely ruled out so a physician should not give the drug to a pregnant woman unless it is clearly needed. The regulation [11] does not state what clearly needed means. Drug manufacturers may only place drugs that have undergone human and animal studies in category A and the label must state that fact. Finally, a category A label must describe any available data on the development of children born to women who took the drug during pregnancy [5].

Under the 2006 Physician Labeling Rule, a category B label indicates that animal studies demonstrated that the drug poses no risk to an animal fetus [9] or pregnant animal mother but that there were no studies performed on pregnant human women. A category B label must have a statement about the type of animal studied and the scale of the dose relative to the human dose. The Physician Labeling Rule also requires that the label states that animal studies do not always indicate a human reaction, and so the drug should only be prescribed if clearly needed. A definition of what clearly needed means is not included. A category B label must also describe any available data on the development of children born to women who took the drug during pregnancy [5].

According to the FDA, drugs placed in category A and B by the 2006 Physician Labeling Rule pose relatively little risk to pregnant women. Categories C, D, and X indicate more risk. Category C indicates that animal studies had demonstrated that the drug was associated with adverse effects on an animal fetus [9], but that no human studies had been performed. According to theregulation [11], when prescribing category C drugs, physicians should consider that the benefit of the drug might outweigh the risks. The Physician Labeling Rule states that drug manufacturers must include a statement on a category C drug label indicating researchers know that a drug is harmful in animal studies at a specified dose. Like categories A and B, the category C label must describe any available data on the development of children born to women who took the drug during pregnancy [5].

The 2006 Physician Labeling Rule states that categories D and X indicate higher levels of drug-associated risk to thefetus [9]. Category D labels must state that there is evidence of fetal risk based on human studies or investigational experience. A category D drug label must also state that the drug is only suitable for use in lifesaving measures or if safer drugs are unavailable. According to the Physician Labeling Rule, if a drug falls under category D, its label must state that researchers know that drug will cause fetal harm when a pregnant woman takes it. Furthermore, the regulation [11] requires the label to include a statement saying that doctors must tell women who become pregnant that the drug is not safe for use during pregnancy [5].

A category X label indicates the highest level of risk. According to the 2006 Physician Labeling Rule, a drug with a category X label demonstrated positive evidence of fetal risk and the risks of using the drug are so severe that they outweigh the benefits of using the drug. The regulation [11] requires drugs to have a label stating that scientists know that the drug will cause fetal harm when administered to a pregnant woman. Additionally, the Physician Labeling Rule requires that drug manufacturers categorize and label any drug that induces abortion [12] as category X.

After describing the regulations for drugs used by pregnant women, Section 8 details drug label rules for drugs used by women during labor and delivery. The “Labor and Delivery” section requires specific labels for drugs used during labor or delivery. The section requires a drug label to include a description of the available information about the effect a drug could have on the pregnant woman or the fetus [9]. The written description must include information about how the drug might impact the duration of labor or delivery when the mother takes the drug during labor or delivery. The label must also include information about the likelihood of a doctor needing to use forceps during delivery, as well as the likelihood that a newborn would need to be resuscitated if the mother took the drug during labor or delivery. If there is information about the development and maturation of a child whose mother took the drug during labor or delivery, drug manufacturers must also include that in in the “Labor and Delivery” section of the label. Drug manufacturers must also state if there is no data available.

The 2006 Physician Labeling Rule also requires information in the “Nursing Mothers” section to detail the risks of drugs prescribed to mothers who are breastfeeding their infants. The “Nursing Mothers” section only requires specific labeling if the drug is known to be absorbed into the bloodstream and excreted in human milk. The 2006 regulation [11] outlines three distinct scenarios in the nursing mother section. The first scenario applies if the drug is absorbed into the mother’s bloodstream, if there was data demonstrating the drug is excreted in breast milk, and if there is data demonstrating potential remote risk to the nursing infant. The next scenario applies if the drug is absorbed into the bloodstream, is known to be excreted in milk, and there is a demonstrable risk to the nursing infant. Depending on the scenario, drug manufacturers must include different subheadings on the label. The 2006 Physician Labeling Rule includes a fill-in-the-blank statement regarding the potential for human risk to be placed on the drug label. Drug manufacturers must use the statements word-for-word. That subheading does state that physicians should use caution when prescribing that drug to a nursing woman. Finally, the last scenario applies if a drug is absorbed into the bloodstream, but scientists are unsure if it is excreted in breast milk. Under that subheading, the drug label must indicate that physicians should use caution in prescribing that drug as well as that there was insufficient data to explicitly say whether the drug is excreted in breast milk.

Many physicians have criticized the 2006 Physician Labeling Rule. The FDA’s Pediatric Advisory Committee asserted that the labels required by the 2006 Physician Labeling Rule were overly simplistic and could lead to physicians or patients misinterpreting information. During the period of public comment, several groups criticized the pregnancy [5] categories. The Teratology Society did not support the use of standardized categories and asserted that the labels would not give people an accurate understanding of the risks associated with certain drugs. The American College of Obstetricians [13] and Gynecologists, or ACOG, indicated that the pregnancy [5] categories were confusing and unhelpful for patients and physicians. ACOG also requested that the FDA replace pregnancy [5] categories with written sections. As of 2018, the FDA replaced the letter categories in the “Pregnancy” section with narrative descriptions and restructured the sections to include “Lactation” and “Males and Females of Reproductive Capacity.”

Sources

1. Feibus, Karen “FDA’s proposed rule for pregnancy [5] and lactation labeling: improving maternal child health through well-informed medicine use.” *Journal of Medical Toxicology* 4 (2008): 284–288.
2. Food and Drug Administration [4]. *Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling; Final Rule.* Washington, DC: GPO, 2006. https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm427798.pdf [14] (Accessed March 27, 2018).
3. Food and Drug Administration [4]. *Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling.* Washington, DC: GPO, 2014. https://www.gpo.gov/fdsys/pkg/FR-2014-12-04/pdf/2014-28241.pdf [15] (Accessed November 03, 2017).
4. Food and Drug Administration [4]. “Guidance for Industry: Labeling for Human Prescription Drug and Biological products – Implementing the PLR Content and Format Requirements.” Food and Drug Administration [4]. https://www.fda.gov/downloads/drugs/guidances/ucm075082.pdf [16] (Accessed November 03, 2017).
5. Food and Drug Administration [4]. “The Pregnancy and Lactation Labeling Rule (PLLR).”Food and Drug Administration [4]. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf [17] (Accessed November 03, 2017).
6. Food and Drug Administration [4]. “Questions and Answers on the Pregnancy and Lactation Labeling Rule.”Food and Drug Administration [4]. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093311.htm [18] (Accessed November 03, 2017).
7. Teratology Society Public Affairs Committee, letter to Food and Drug Administration [4], August 26, 2008. https://www.regulations.gov/document?D=FDA-2006-N-0515-0050 [19] (Accessed November 04, 2017).
8. Vargesson, Neil. “Thalidomide-induced teratogensis: History and mechanisms.” *Birth Defects Research* 105 (2015): 140–156. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737249/pdf/BDRC-105-140.pdf [20] (Accessed March 27, 2018).

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