

# [US Food and Drug Administration's Requirements on Content and Format for Labeling for Human Prescription Drugs Rule \(1979\)](#) <sup>[1]</sup>

By: Meek, Caroline Keywords: [drug label](#) <sup>[2]</sup> [drug law](#) <sup>[3]</sup> [1979 Labeling Rule](#) <sup>[4]</sup> [Pregnancy](#) <sup>[5]</sup> [drug safety](#) <sup>[6]</sup>

The Food and Drug Administration's Content and Format for Labeling for Human Prescription Drugs Rule, or the 1979 Labeling Rule, first assessed the risk of prescription drugs in pregnant women and fetuses. Prior to 1979, drug labels were only required to state true information, but there were no requirements for content or format. The 1979 Labeling Rule established a required format for all prescription drug labels, which included assigning drugs to a risk category for pregnant and lactating women. Those risk categories indicated what level of risk a drug posed to a pregnant woman, fetus <sup>[7]</sup>, or breastfeeding infant based on experimental and case studies. The 1979 Labeling Rule sought to improve the safety and efficacy of drugs and established the first classification system for identifying the risks prescription drugs posed to pregnant women, fetuses, and breastfeeding infants.

In the US, the FDA regulates drug manufacturers to ensure the safety and efficacy of drugs. In the first step of that 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.

In 1906, the US government regulated the labels of food and drugs by passing the Food and Drugs Act. The Food and Drugs Act prohibited anyone from selling mislabeled or dangerous drugs in the US. In 1938, Congress revised the [regulation](#) <sup>[8]</sup> of drugs with the passage of the Federal Food, Drug, and Cosmetic Act. That act required drug manufacturers to demonstrate that their drugs were safe in clinical studies before they marketed those drugs to the American public. In 1962, the drug thalidomide was marketed to pregnant women in western Europe as way to reduce nausea. The children of mothers who took thalidomide while pregnant were often born with severe [birth defects](#) <sup>[9]</sup>, including missing or deformed limbs. That same year, 1962, Congress passed the Kefauver-Harris Drug Amendments to improve the safety and efficacy of drugs in the US. Those amendments required drug manufacturers to prove that their drugs were effective before they could market those drugs to the public. By the early 1970s, pregnant women, fetuses, and breastfeeding infants were still experiencing negative effects associated with several other drugs. The FDA continued to revise drug regulations in response.

In the early 1970s, the FDA drafted a rule that established regulations for the labeling of all drugs which included a focus on drugs specifically used by pregnant and lactating women. In March 1974, the FDA released a draft of the rule that would later become the 1979 Labeling Rule. The FDA placed the draft rule on display publicly in the FDA office in Silver Spring, Maryland. The FDA also circulated the draft rule among drug manufacturers, medical associations, individual physicians, and everyone who requested it. The public, physicians, drug manufacturers, and other members of the medical community submitted over 150 comments on the draft rule. Several commenters stated that the information put on drug labels could be used in a medical malpractice lawsuit. Some commenters specifically objected to the classification of [pregnancy](#) <sup>[10]</sup> warnings, stating that researchers could not accurately estimate what risk drugs might pose to pregnant women and fetuses. Donald Kennedy, then commissioner of the FDA, addressed the comments, noting that the FDA intended the 1979 Labeling Rule to give doctors an accurate and efficient method to access the information they need to prescribe drugs safely and effectively. He then wrote that the care of pregnant women requires very specific information and consistency within drug labels. After Kennedy reviewed and incorporated public feedback, the FDA published the final version of the 1979 Labeling Rule on 26 June 1979.

With the 1979 Labeling Rule, the FDA regulated what information manufacturers must include on a drug label and the way that information was formatted. The rule regulated the label on a drug bottle, as well as the foldable handout that comes with a prescription drug or inside the container of an over-the-counter drug. In the final draft of the rule, the FDA separated labeling requirements into two sections, general and specific. In a section entitled General Requirements, the new labeling rule required that drug labels include an accurate summary of scientific information about a drug and its mechanism, or how it works in the human body. They specified that this section could not be written to sound like an advertisement. The [regulation](#) <sup>[8]</sup> also required that labels prioritize human research studies over animal research studies and that any conclusions made based on those studies must be supported by substantial evidence. The [regulation](#) <sup>[8]</sup> also established headings for specific information that the FDA wanted manufacturers to include on drug labels. Those headings included when a drug should be used, when a drug should not be used, warnings of adverse effects, precautions, dosages, and appropriate response in the case of an overdose. The [regulation](#) <sup>[8]</sup> also suggested optional supplementary headings addressing clinical studies and references. Under the new

[regulation](#)<sup>[8]</sup>, if a drug manufacturer changed a drug label, the manufacturer had to include the dates of the revision immediately after the last section of the label.

The 1979 Labeling Rule established general requirements for drug labels on every drug sold in the US. The FDA also mandated that certain drug labels must comply with more specific requirements in a section entitled Specific Requirements. Those requirements addressed situations unique to certain kinds of drugs. For example, a drug intended for children required a label about the drug's use and risk in children. There were eleven specific sections. One section was specific to [pregnancy](#)<sup>[10]</sup>, lactation, and labor and delivery.

Under the Specific Requirements heading, the new labeling rule required that manufacturers detail the chemical information of a drug, including its structure and pH, or how acidic it was. Manufacturers also had to include a summary of how the drug worked in the human body on the label. If that information was unknown, the label had to include a description of how a drug worked in laboratory experiments or in animals. The second heading also required that manufacturers included data that demonstrated the drug did what manufactures claimed. If that information was not known, the second heading required that drug labels included a sentence that stated there was not sufficient information from human studies to determine whether the drug did what manufacturers claimed.

Next in the specific requirements section, the 1979 Labeling Rule required a third heading for when and how a drug should be used. That heading required drug labels to include which specific ailment manufacturers intended that drug to treat. For example, the drug label for an antibiotic that manufacturers intended to treat pneumonia had to include a statement that the drug was intended to treat pneumonia. Additionally, manufacturers had to state that a drug's intended use was supported by substantial scientific evidence under the third heading. Finally, the FDA required that the third heading include information about specific tests that doctors could use to determine if a patient was a good candidate for the drug.

The next specific heading covered the contraindications for the drug, or instances when a patient should not use a drug. In that heading, drug manufacturers had to detail situations in which the risk of a patient using the drug outweighed any possible benefit. In the following section, the 1979 Labeling Rule required that manufacturers include further details about potential adverse reactions, safety hazards, and limitations in use of the drug. The FDA indicated that those warnings were intended to be brief and did not need to be based solely on human data.

According to the 1979 Labeling Rule, under the next required heading, drug labels had to review drug precautions, or the procedures doctors had to follow before administering the drug to patients. The FDA ruled that drug manufacturers had to include information for patients to read, suggestions about laboratory tests that doctors could use to determine if a patient could have a negative reaction, a description of long term studies showing whether the drug could possibly be carcinogenic, and precautions for [pregnancy](#)<sup>[10]</sup>. The precautions for [pregnancy](#)<sup>[10]</sup> subsection of the 1979 Labeling Rule was the first instance in which drug labels were regulated by the FDA in relation to [pregnancy](#)<sup>[10]</sup>. Prior to the 1979 Labeling Rule, drug labels were not required to have information about their use and effects in pregnant women.

Drug manufacturers only had to include the precautions for [pregnancy](#)<sup>[10]</sup> subsection on the label if the drug was known to be absorbed into the bloodstream. Drugs absorbed into the bloodstream can be transferred from a pregnant woman to her [fetus](#)<sup>[7]</sup> through their shared blood supply. If the drug did not demonstrate any adverse effects in pregnant women, drug manufacturers did not need to include the [pregnancy](#)<sup>[10]</sup> subsection. The [pregnancy](#)<sup>[10]</sup> subsection included three general topics for inclusion on the drug label: risk of teratogenic effect, risk of non-teratogenic effect, and drugs excreted in breast milk. For each category, the [regulation](#)<sup>[8]</sup> required that drug labels describe the data upon which manufacturers made their conclusions.

Under the section regarding teratogenic effects, drugs were classified into five categories, A, B, C, D, and X. Teratogens are substances, including drugs, that can cause [birth defects](#)<sup>[9]</sup>. Low risk drugs belonged in category A, while high risk drugs belonged in category X. A category A drug was one that demonstrated no risk to the [fetus](#)<sup>[7]</sup> during the first twelve weeks of [pregnancy](#)<sup>[10]</sup>. For a drug in category A, the [regulation](#)<sup>[8]</sup> required that manufacturers include a fill-in-the-blank sentence with space for the name of the drug and the studies that supported that the drug was safe to use. The [regulation](#)<sup>[8]</sup> also required labels to say that physicians should use the drug with good judgment because animal studies could not completely rule out risk in [humans](#)<sup>[11]</sup>. Finally, the [regulation](#)<sup>[8]</sup> required a category A drug's label to include a description of the growth and maturation of a child born to a mother who had taken the category A drug. The FDA used category A to make physicians aware that a drug did not pose any known risk to a pregnant woman or her [fetus](#)<sup>[7]</sup>.

Next, the [regulation](#)<sup>[8]</sup> detailed the labeling requirements for drugs that posed slightly more risk to [afetus](#)<sup>[7]</sup>, category B drugs. Category B drugs included drugs that had been tested in animals and did not show any risk to the [fetus](#)<sup>[7]</sup>, but, at the time of manufacturing, had not been tested in [humans](#)<sup>[11]</sup>. The [regulation](#)<sup>[8]</sup> provided a fill-in-the-blank sentence that stated that reproduction studies had been performed in pregnant animals at a dose greater than what would usually be used in [humans](#)<sup>[11]</sup>, and that those studies demonstrated no increased risk to the animal fetuses. The [regulation](#)<sup>[8]</sup> also required that the label state that there were no human studies available and that animal studies were not always indicative of human response, and so the drug should only be prescribed if it was clearly needed. Under the FDA rule, manufacturers could also label a drug as category B if animal studies had been performed and demonstrated risk to the [fetus](#)<sup>[7]</sup>, but human studies had also been performed and demonstrated no risk. The [regulation](#)<sup>[8]</sup> required that the label specifically state that, despite animal studies demonstrating risk,

the risk to a human fetus<sup>[7]</sup> appeared to be remote. The FDA used category B to make physicians aware that a drug was mostly safe, but could potentially pose some risk to a pregnant woman or her fetus<sup>[7]</sup>.

Next, the 1979 Labeling Rule addressed drugs that posed a moderate amount risk to fetus<sup>[7]</sup>. Those drugs were labeled as category C. The regulation<sup>[8]</sup> defined category C drugs as those drugs for which animal studies demonstrated that the drug had negative effects on a fetus<sup>[7]</sup>, but no human studies had been performed to confirm that conclusion. The regulation<sup>[8]</sup> required a description of any available data about the growth and maturation of a child born to a woman who had taken a category C drug to be included on the label. The FDA used category C to make physicians aware that the risk of a specific drug, when taken during pregnancy<sup>[10]</sup>, was relatively unknown, and thus physicians should only prescribe that drug when a safer drug is not available.

Next, the 1979 Labeling Rule addressed drugs that sometimes posed a significant amount of risk to the fetus<sup>[7]</sup>, but whose benefit for the mother justified their use. Such drugs were labeled category D. For the FDA to categorize a drug as D, studies had to show that a drug posed risks to a human fetus<sup>[7]</sup>, but that the benefit of the drug might outweigh the risk. For example, a safer alternative might not be available and, in that case, a category D drug may be permissible to use. The regulation<sup>[8]</sup> stated that category D drugs should only be given as lifesaving measures or in cases of serious disease. The FDA used category D to make physicians aware that that they should only prescribe a drug if it was clearly needed.

The final category of drug in the 1979 Labeling Rule was X. A drug placed in the X category had the same level of risk as a class D drug except that the risks of giving the class X drug clearly outweighed the benefits. For example, if a safer alternative existed and the drug might cause a birth defect, that regulation<sup>[8]</sup> required manufacturers to label the drug as category X. The FDA used category X to make physicians aware that a drug should not be prescribed to a pregnant woman.

After the section describing the labeling requirements for drugs that cause birth defects<sup>[9]</sup>, the FDA included a statement about instances in which the usual categories do not apply. Non-teratogenic drugs, or drugs that do not cause birth defects<sup>[9]</sup>, did not require the risk category label per the 1979 Labeling Rule. Those drugs required a different label that would indicate a drug posed a different kind of risk. For example, drugs that could cause withdrawal symptoms or low blood sugar in an infant upon birth were included in the non-teratogenic drugs section.

After the pregnancy<sup>[10]</sup> subheading, the 1979 Labeling Rule included a labor and delivery section. Under that section, the regulation<sup>[8]</sup> required that manufacturers indicate on a drug label if that drug could possibly interfere with a woman's labor or delivery. Some physicians attributed the need for forceps delivery or infant resuscitation upon birth to the utilization of particular drugs during labor. The regulation<sup>[8]</sup> required drug manufacturers to specify on the label if there were documented instances of such events.

The next section required by the 1979 Labeling Rule outlined guidelines for the use of drugs excreted into breast milk. The regulation<sup>[8]</sup> categorized drugs used by nursing mothers into three groups: drugs that the body absorbed into the bloodstream but were not excreted in breast milk, drugs that the body absorbed into the bloodstream and were excreted in breast milk, and drugs that were not absorbed into the bloodstream. For each scenario, the regulation<sup>[8]</sup> required labels to state that taking any drug while breastfeeding could be dangerous, and that physicians should assess the importance of a drug to the mother before prescribing such a drug.

After the pregnancy<sup>[10]</sup>, labor and delivery, and nursing mothers sections, the regulation<sup>[8]</sup> required an additional section that identified adverse drug reactions. In the regulation<sup>[8]</sup>, the FDA defined an adverse reaction as any undesirable effect associated with use of a drug. The regulation<sup>[8]</sup> required that drug labels include information about the frequency and severity of adverse reactions to drugs, as well as the organs affected. It provided a fill-in-the-blank sentence with space for the name of a drug, the reported reactions, and the likelihood of a consumer experiencing an adverse reaction. The FDA noted in the 1979 Labeling Rule that the drug reactions section only applied to non-fatal reactions, and if a reaction was fatal, then manufacturers should place that information in earlier sections.

After the drug reactions section, the regulation<sup>[8]</sup> mandated a final section on drug abuse and dependence. The regulation<sup>[8]</sup> required government-regulated drugs like narcotics to include information about drug tolerance and drug dependence on the label. The regulation<sup>[8]</sup> also required manufacturers to include procedures about how to treat patients who stop taking a drug abruptly on the label. Additionally, the regulation<sup>[8]</sup> required that a label include information about overdose of a drug. For example, the label of a drug had to include specific information about the symptoms and laboratory studies associated with a serious overdose of that drug.

The 1979 Labeling Rule went into effect on 26 December 1979, seven months after its initial publication. Any new drugs manufactured after 26 December 1979 had to comply with the requirements set in the new rule.

The medical community stated that the pregnancy<sup>[10]</sup> categories established by the Content and Format for Labeling for Human Prescription Drugs were not useful for physicians. Some comments on the formal rule requested simplification of the pregnancy<sup>[10]</sup> categories. The commissioner even conceded that the number of categories could be reduced for simplicity. According to George Demaagd, a professor of pharmacy, the risk categories made it difficult for physicians to assess the risks and benefits

associated with drugs when prescribing them to pregnant and lactating women. The FDA amended the Content and Format for Labeling for Human Prescription Drugs in 2006 and again in 2014. In 2006, the [pregnancy](#)<sup>[10]</sup> categories were modified. In 2014, the FDA discontinued the ranking system and instead required labels to use a narrative structure for [pregnancy](#)<sup>[10]</sup> labeling.

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## Subject

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## Topic

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