

FDA Proposes Rule Change to Pregnancy and Lactation Labeling: No More ABCs?

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On May 28, 2008, the U.S. Food and Drug Administration announced proposed changes to the current rule governing prescription drug labeling. The new rule would eliminate the pregnancy category system and a "Labor and Delivery" subsection and replace them with specified subsections detailing the risks associated with the specific drug.¹

Implemented in 1979, the current system assigns the relative risk-benefit of drug use

Table 1. Current Pregnancy Categories²

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

during pregnancy to five categories.³ (See Table 1.) This system applies only to drug use during pregnancy, not lactation. Additionally, the risk to the fetus between categories is not necessarily comparative.⁴ As noted in the category descriptions in Table 1, category assignment is based on risk to the fetus, the potential benefit of therapy, and the available data. Currently, fetal risk is only one factor in category determination, and risk may actually be comparable in categories C, D, and X. In focus groups and public meetings hosted by the FDA, stakeholders have stated that the current system "leads to an inaccurate and overly simplified view of these risks, and does not facilitate updating of labeling as new information becomes available."¹

To mitigate these limitations, the proposed rule change eliminates the category system. In its place, the pregnancy and lactation sections are subdivided into three sections: risk summary, clinical considerations, and data. Each section is defined as follows:¹
Risk summary: provides a conclusion about the risk of drug therapy.
Clinical considerations: includes information on inadvertent exposure, recommendations about dosage adjustment, timing, and exposure of drug, and potential complications.
Data: describes the available human and animal data supporting the other sections.

The FDA's proposed timeline for implementation complies with the physician labeling rule.⁵ New drug applications approved before June 29, 2001 would not have to implement the new content requirements; they would have to remove the pregnancy category within three years of the effective date of the final rule. For drug applications approved after June 29, 2001, the implementation would follow the timeline outlined in Table 2.⁵

Table 2. Proposed Implementation Timeline⁵

Applications Required To Conform to New Requirements	Time by Which New Content Must Be Submitted to FDA
<i>New or Pending Applications:</i>	
Applications submitted on or after the effective date of the pregnancy final rule	Time of submission
Applications pending on the effective date of the pregnancy final rule	4 years after the effective date of pregnancy final rule or at time of approval, whichever is later
<i>Approved Applications Subject to the Physician Labeling Rule:</i>	
Applications approved any time from June 30, 2001, up to and including June 29, 2002, and from June 30, 2005, up to and including June 29, 2007	3 years after the effective date of pregnancy final rule
Applications approved any time from June 30, 2007, up to and including the effective date of the pregnancy final rule	4 years after the effective date of pregnancy final rule
Applications approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of pregnancy final rule

The proposed rule was published in full in the *Federal Register* on May 29, 2008 and is open to public comment for the following 90 days.⁵ Electronic comments may be submitted via the Federal Documents Management System/eRulemaking portal at www.regulations.gov.¹

Commentary

If implemented, the transition period will challenge clinicians. For five years, two physician labeling systems will exist and some drugs will only remove the pregnancy category without revising their labeling. Some clinicians may resist the new system and cling to the letter category system due to its familiarity and their comfort level. Some may try to devolve the new format back into a category system to make it more convenient for daily practice. However, to force these data back into a category once released from such limiting boundaries, would defeat the purpose of revision.

Additionally, physician labeling is not the only source of information on the effects of drugs in pregnancy and lactation. Information in physician labeling is manufacturer supplied and is approved by FDA for distribution; however, other reputable references exist, such as *Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk*, and offer information beyond that available via approved labeling.

The breadth and depth of pregnancy and lactation data vary greatly among drugs, and safety data in pregnancy does not dictate safety in lactation or vice versa. The FDA's effort to encourage clinicians to consider each agent individually is a positive step, but will require many clinicians to rethink their approach to drug use in pregnant or lactating women. Patient and drug factors must be assessed when considering drug therapy in these populations.

References

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3. Pregnant women to benefit from better information. FDA Consumer Health. U.S. Food and Drug Administration. May 28, 2008. <http://www.fda.gov/consumer/updates/pregnancy052808.html>. Accessed July 15, 2008.
4. Summary of proposed rule on pregnancy and lactation labeling. U.S. Food and Drug Administration. http://www.fda.gov/cder/regulatory/pregnancy_labeling/summary.htm. Accessed July 15, 2008.
5. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. *Federal Register*. 2008;73(104):30831-30868. Available from: <http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2006-N-0515>. Accessed July 15, 2008.