



New Labeling for Pregnant Populations

FDA proposes changes to drug labels for pregnant, breast-feeding women

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On May 29, 2008, the U.S. Food and Drug Administration (FDA) published a proposed rule to amend the regulations governing the content of the "Use in Specific Populations" section of the labeling for prescription drugs and biological products. Specifically, the proposed rule would require that prescription drug and biological product labeling provide extensive information on the effects of a given product when used during pregnancy or by breast-feeding mothers. The proposed rule is intended to provide more meaningful information to allow healthcare providers and women of child-bearing age to make better decisions about the use of drugs and biologics during pregnancy or lactation.

In response to concerns about the usefulness of the existing "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of prescription drug product labeling, FDA held a Part 15 hearing and two advisory committee meetings on the topic. The Agency also consulted with focus groups and the public to gather comments on how these regulatory subsections could be improved. The comments FDA collected reflect a commonly held opinion that the current product labeling lacks clarity and often fails to provide meaningful clinical information about drug exposure during pregnancy and lactation, and that labeling is not designed to address either inadvertent drug exposure in early pregnancy or potential consequences of drug discontinuation during the course of a pregnancy that was prescribed to the mother for a chronic condition. The proposed rule seeks to address these concerns, among others.

The proposed rule would amend current regulations found at Sections 201.56(d)(1), 201.57(c)(9)(i)-(iii), and 201.80(f)(6)-(8) of Title 21 of the U.S. Code of Federal Regulations dealing with the labeling requirements regarding the effects of drugs and biologics in special populations, namely pregnant women and nursing mothers. Under the current labeling requirements, prescription drugs must include a "Pregnancy" subsection unless it is not absorbed systemically and is not known to indirectly harm a fetus. This subsection relays information about the product's teratogenicity and its effects on reproduction and pregnancy, including a summary of clinical studies and data on its effects on later growth, development, and maturation of the child, if available. If a Pregnancy subsection is provided, it includes the product's "pregnancy category." The existing pregnancy categories — A, B, C, D, or X — designate the reproductive and developmental risks associated with the product. Category A products have not been shown to increase the risk of fetal abnormalities when administered during a given trimester of pregnancy. Category X drugs, on the other hand,

exhibit positive evidence of risk to the fetus that outweighs any possible benefit. Categories B, C, and D represent intermediate levels of risk balanced against the benefits of using the product. The required labeling warnings increase in severity as one moves from category A through X.

Under the proposed rule, the system of letter classification for drugs and biological products would be eliminated. FDA asserts that the current classification system is "confusing" and "not adequate to effectively communicate risk of reproductive and developmental toxicity." FDA explained in the commentary published with the proposed rule that "[a] major problem . . . is that the categories convey the incorrect impression that developmental risk increases from category A to B to C to D to X when, in fact, the criteria for inclusion in the categories . . . also consider risk weighed against benefit." Thus, drugs with similar risk levels could be categorized differently because a given drug is judged to possess greater benefits in a risk-benefit analysis. FDA also stated that the classification system created the incorrect impression that drugs within a certain category have similar potential to cause developmental toxicity. Finally, another problem with the current classification system is that drugs with known risks and drugs with no known risks actually may be placed in the same category.

Under the proposed rule, § 201.57 would be amended to merge the "Pregnancy" and "Labor and Delivery" subsections of the "Use in Specific Populations" labeling section into a single "Pregnancy" subsection. The "Nursing Mothers" subsection would be renamed "Lactation."

The "Pregnancy" subsection of prescription drug labeling would be required to provide the following information: (1) pregnancy exposure registry information (if applicable); (2) general statement about background risk of fetal developmental abnormalities; (3) fetal risk summary; (4) clinical considerations; and (5) data. The "Pregnancy" subsection would be required for all drugs under the proposed rule. This is a change from the current regulations, which permit the subsection to be omitted for drugs that are not absorbed systemically and not known to have a potential for indirect harm to the fetus.

- **Pregnancy Exposure Registry Information:** Pregnancy exposure registry information would be required whenever a pregnancy exposure registry exists for a given drug. Pregnancy exposure registries are studies that collect information on women taking a medical product while pregnant.

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The proposed rule would require that the labeling for a drug product provide the information (e.g. telephone number) needed to enroll in a registry or to obtain information from the registry.

- **General Statement about background risk of fetal developmental abnormalities:** This part of the “Pregnancy” subsection would provide information on the background risks of developmental abnormality that are inherent in human pregnancy. This information is needed to emphasize that risk information provided about a drug product describes a drug’s potential to increase the risk of fetal abnormalities above the background risk level.
- **Fetal Risk Summary:** The fetal risk summary would provide a description of the drug’s risks that includes a risk conclusion, a narrative description of the risk, and reference to any relevant contraindications or warnings and precautions. For example, a risk conclusion might state, “[h]uman data indicate that theophylline increases the risk of cardiac abnormalities.” The narrative description of the risk would include the specific developmental abnormality associated with a drug, and the “incidence, seriousness, reversibility, and correctability of the abnormality.” The effects on the risk of dose, exposure duration, and timing of exposure

should also be described. Finally, the “contraindications” portion of the fetal risk summary would seek to provide information about when a drug should not be used because the risks outweigh the benefits to the mother or to the fetus.

- **Clinical Considerations:** This portion of the “Pregnancy” subsection is intended to provide healthcare providers with information on how to deal with situations where women were inadvertently exposed to the drug during pregnancy; prescription decisions must be made for pregnant women; and prescription decisions must be made during labor and delivery.
- **Data:** The “Data” subsection would “provide a brief overview of the data that are the basis for the fetal risk summary and the clinical considerations portion of the labeling.” Human and animal data must be presented separately, with human data being presented first.

The “Lactation” subsection of prescription drug labeling would be required to provide the following information: a risk summary; clinical considerations; and data.

- **Risk Summary:** This portion of the “Lactation” subsection would summarize the drug’s impact on milk production; information known about the presence of the drug in human milk; and the effects on the child feeding on the affected milk.
- **Clinical Considerations:** This portion of the “Lactation” subsection would discuss ways to minimize the exposure of the child feeding on the affected milk, the potential effects of the drug on the child feeding on the affected milk, and any dosing adjustments during lactation.
- **Data:** The “Data” portion of the “Lactation” subsection would “provide an overview of the data that are the basis for the risk summary and the basis for the clinical considerations component.”

Under the proposed rule, new and recently approved products would be required to submit labeling content in compliance with the amended regulations. For “older” products, those which have already been approved, the application holders would be required to file a supplemental application to obtain approval for new labeling that satisfies the new regulations when they become effective. FDA is proposing an implementation schedule that would give all affected parties, *except* those who submit an application on or after the date the rule becomes effective, a minimum of three years after the effective date of the pregnancy final rule to submit labeling with the new content.

In summary, the rule proposes to enhance the information contained in the prescription drug labeling to improve the quality of its contents as it relates to treatment of the special populations. FDA believes that providing up-to-date information on the safe and effective use of prescription drugs during pregnancy and lactation in a standardized format will make labeling a more reliable resource for healthcare providers to consult when seeking prescription drug information for their pregnant and lactating patients. ■