FDA/CDER SBIA CHRONICLES
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Drugs in Pregnancy and Lactation: Improved Benefit-Risk Information

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Until now, the information that FDA required in prescription product labeling regarding pregnancy and lactation was not always useful and was often misinterpreted. This is about to change… FDA has published a rule that provides a framework for clearly communicating information on the benefits and risks of using a drug during pregnancy and lactation.

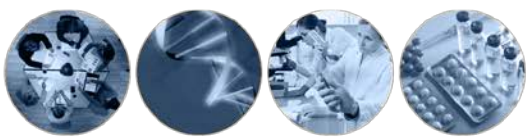
Conveying the benefits and risks of drug products in the prescription drug labeling, also known as the package insert, allows health care providers to determine whether or not to use a particular product and how best to use it safely. This is especially important during pregnancy or lactation. In December, FDA published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR). This rule sets standards for how information about using medicines during pregnancy and breastfeeding is presented in the labeling of prescription drugs and biological products. FDA also issued a draft guidance for industry to assist drug manufacturers in complying with the new labeling content and format requirements. FDA has posted quite a bit on this topic, but we hope that this quick two-page summary will help you obtain an overview of the requirements, along with where to find detailed information.

Highlights of the PLLR include:

1. The pregnancy letter categories – A, B, C, D and X will be replaced by a narrative risk summary based on available data. Although the letter category system has been in place since 1979, FDA learned from experience and stakeholder feedback that these letter categories are often misinterpreted as a 'grading system.' The pregnancy letter designations were classified based on what was known from human and animal data. These letter categories were overly simplistic, and did not effectively communicate the risk a drug may have during pregnancy and lactation. Heavy reliance upon pregnancy categories often led to misinterpretation of the information, making prescribing decisions based on the pregnancy category rather than an understanding of the underlying information that informed the assignment of the pregnancy category. FDA believes that a narrative structure for pregnancy labeling, rather than a category system, is best able to capture and convey the potential risks of drug exposure based on animal or human data, or both.

2. The current **Pregnancy** and **Labor and delivery** subsections are merged into a single **Pregnancy** subsection (8.1) of labeling. Additionally, if there is a scientifically acceptable pregnancy exposure registry for the drug, this subsection must contain a specified statement about the existence of the registry, followed by contact information needed to enroll or to obtain information about the registry. Pregnancy exposure registries collect and maintain data on the effects of approved drugs that are prescribed to and used by pregnant women.

The **Pregnancy** subsection is re-organized to include a summary of the risks of using a drug during pregnancy. This risk summary replaces the current pregnancy letter category. For drugs that are absorbed systemically, the "Risk Summary" must include statements based on the risk of adverse developmental outcomes from all relevant data sources. When there is relevant information to help health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy, it is included under a new heading called Clinical Considerations. This could include information on disease-associated maternal and/or embryo/fetal risk, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, and fetal/neonatal adverse reactions. Information on the effects of the drug on labor or delivery is also placed under this heading. The data supporting the risk summary are summarized under the Data heading of the new Pregnancy subsection.



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3. The **Nursing Mothers** subsection was renamed the **Lactation** subsection (8.2), and provides information, when known, about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant. This subsection must also include, to the extent information is available, relevant information concerning ways to minimize drug exposure in the breast-fed child in certain situations. It should also reference available interventions for monitoring or mitigating the adverse reactions presented elsewhere in the labeling. In addition, the labeling must also include pertinent information about the data that are the basis for the risk summary and clinical information included in this section.

4. The **Females and Males of Reproductive Potential** subsection (8.3), new to the labeling, includes information, when necessary, about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the use of the drug. This new subsection creates a consistent place in labeling for information for both females and males of reproductive potential. The location of this information in the current labeling has not been consistent.

In addition, the PLLR calls for inclusion of updated information in the labeling. Data from human studies is rarely available at the time a drug is first approved. However, data may become available from various sources, including well-conducted studies published in the medical literature about the use of prescription drugs and biological products during pregnancy and breast-feeding. Another source of data could be from pregnancy exposure registries, which are conducted by some companies to collect information on the effects of their approved drugs when those drugs are used by pregnant women to treat a medical condition.

Why: You may be asking why FDA has now decided to change this system when it has been in place for decades. This rulemaking is part of a broad effort by the Agency to improve the content and format of prescription drug labeling. The PLLR amends the Physician Labeling Rule (PLR) that deferred revisions to these subsections when the PLR was published in 2006. FDA obtained extensive stakeholder input as part of the rulemaking process, including public hearings and advisory committee meetings, focus groups, and the issuance of a proposed rule in 2008 and the opening of a docket to receive comments from the public.

When: The PLLR labeling changes go into effect June 30, 2015. Prescription drugs and biologic products submitted after June 30, 2015, will use the new format immediately. Applications that are pending with the agency on June 30, 2015 must comply within four years of the effective date, or at the time of approval, whichever is later. Previously approved prescription products that were approved on or after June 30, 2001 have a phased-in implementation schedule from 3-5 years, as outlined in Section IV of the PLLR. Several manufacturers have already incorporated labeling changes in anticipation of the publication of the final PLLR, so many products on the market already have labeling similar to requirements established under the rule. Manufacturers whose products are subject to the rule are responsible for updating labeling when information becomes available regarding the use of their product by pregnant or lactating women.

Guidance: Concurrent with publishing the PLLR, FDA has issued a Draft Guidance for Industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format to assist drug manufacturers in complying with the new labeling content and format requirements. This draft guidance provides recommendations to applicants in developing labeling for new products, revising existing labeling, and implementing the content and format requirements of the PLLR for human prescription drug and biological products.

Note that regarding generic drugs, if the labeling of a reference listed drug (RLD) is updated as a result of the final rule, the abbreviated new drug application (ANDA) labeling must also be revised. The PLLR does not apply to over-the-counter (OTC) medicines.

We hope that you are as excited as we are about making a difference by providing clear and useful information to protect pregnant and breastfeeding mothers and their children!

Cheers,
Renu Lal, Pharm.D.
CDER Small Business and Industry Assistance

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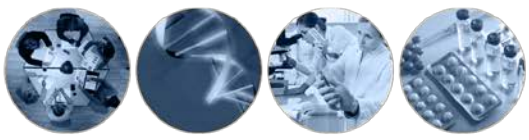

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