The New Pregnancy and Lactation Labeling Rule

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INTRODUCTION

The use of medications in pregnancy and lactation presents a challenge to all health care providers. This is especially true with the long-standing pregnancy risk categories A, B, C, D, and X (Table 1), which make risk–benefit ratio assessment difficult. Numerous medications have been used safely and effectively in pregnancy with minimal risk to the fetus and mother, although the decision to use them is not without apprehension. The availability of more detailed information related to the safety and efficacy of medications in pregnancy and lactation may assist providers and patients in making more evidence-based decisions.[1]

To address the need for updated risk categories, the Food and Drug Administration (FDA) published a final rule entitled *Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling,* which is also known simply as the "Pregnancy and Lactation Labeling Rule" (PLLR), in December 2014.[2,3] Along with the PLLR, the FDA issued a draft document entitled *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format* to serve as a guidance to industry in preparing PLLR-compliant drug applications.[3] The PLLR represents a significant departure from the previously established pregnancy categories, initially implemented in the FDA's 1979 *Labeling for Prescription Drugs Used in Man* regulations.[2,5] These regulations required the assignation of a pregnancy letter category (A, B, C, D, or X) to medications (Table 1).[4] Under the PLLR, these categories are being phased out, which will be discussed later in this article.

DEVELOPING THE PLLR

During the development of the PLLR, the FDA received input from public hearings, focus groups, and advisory committees. Input from these sessions and groups included concerns that the existing pregnancy categories may be misinterpreted or misused and that pregnancy drug labeling lacked clarity. In addition, the groups reported that the categories failed to provide meaningful clinical information about drug exposure during pregnancy and lactation and did not address the potential maternal and fetal consequences of discontinuing needed drug therapy during pregnancy.[2] In the new PLLR, drugs may be placed in the same category but have varying degrees of risk that a single letter category oversimplifies. For example, 60% of all medications assigned a pregnancy category fall into category C. This category includes medications with data supporting adverse effects in animals, as well as medications with no data from animal studies; the older pregnancy category system allows drugs with evidence of risk and those without evidence of risk to be assigned the same category.[5] These previous pregnancy categories are defined not by severity or incidence of risk, but rather by the amount and quality of available data.[2]

Table 1 Pregnancy Categories Prior to New Pregnancy and Lactation Labeling Rule[2]

Category	Risk	Examples
A	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy.	Doxylamine Folic acid Levothyroxine
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women, ***or*** animal reproduction studies have shown adverse effects, but well-controlled studies in pregnant women have shown no adverse effects to the fetus.	Amoxicillin Loratadine Ondansetron
C	Animal reproduction studies have shown an adverse effect on the fetus, ***or*** there are no animal reproduction studies and no well-controlled studies in humans.	Fluconazole Metoprolol Sertraline
D	Positive evidence of fetal risk, but benefits may outweigh risks.	Lisinopril Lithium Phenytoin
X	Positive evidence of fetal risk, and risks clearly outweigh any possible benefit.	Methotrexate Simvastatin Warfarin

The FDA also conducted a mental-models research study in 2009 to understand the treatment decisions of health care professionals prescribing medications to pregnant and lactating women.[6] This mental-modeling approach compared the decision-making process of study participants to what was considered an "expert" model. A total of 54 health care providers were involved in this study. The prescribers were asked by telephone to describe factors that influence their decisions when treating pregnant and nursing women with chronic conditions.[7] The study found that health care providers relied heavily upon pregnancy categories, more so than on additional information found in the product labeling. In addition, prescribers reported they relied on sources other than the labeling to determine the pregnancy category. The study participants suggested ways to improve drug pregnancy labeling, including simplifying the information presented, centralizing the relevant information, and making the information more clinically relevant.[5]

WHAT THE PLLR CHANGES

The PLLR seeks to address the criticisms of the previous labeling system and reform pregnancy labeling with a number

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of changes to all prescribing information.[3] The PLLR will remove the pregnancy letter categories, change and combine sections pertaining to pregnancy and lactation, and add one new section (Table 2).

The previous sections "8.1 Pregnancy" and "8.2 Labor and Delivery" are now combined to form one section, "8.1 Pregnancy." This section will include the following subsections: "Pregnancy Exposure Registry," "Risk Summary," "Clinical Considerations," and "Data." The "Pregnancy Exposure Registry" subsection is required only if such a registry exists for the product and should include information about how to enroll in the registry. The "Risk Summary" subsection should be presented as a narrative and summarize any human, animal, and pharmacological risk data available. It should also include background information regarding the risk of major birth defects and miscarriage in the U.S. general population.[3] The "Clinical Considerations" subsection details disease-associated maternal and fetal risk, relevant dose adjustments, maternal and fetal adverse reactions, and labor and delivery information. The "Data" subsection describes the information used for the "Risk Summary" and "Clinical Considerations" subsections.[3]

The previous section "8.3 Nursing Mothers" now becomes "8.2 Lactation." Similar to the pregnancy section above, "8.2 Lactation" also contains the subheadings "Risk Summary," "Clinical Considerations," and "Data." The "Risk Summary" describes the presence of the drug in human milk and the effects on milk production and the breastfed child, and contains a statement on the risk–benefit ratio related to use. The "Clinical Considerations" section will include information on minimizing exposure and monitoring for adverse reactions.[3]

The new section incorporated into the PLLR is "8.3 Females and Males of Reproductive Potential." This section should be utilized in the following situations: 1) if there are recommendations or requirements for pregnancy testing and/or contraception before, during, or after drug therapy, and 2) if there are human and/or animal data suggesting drug-associated effects on fertility and/or preimplantation loss effects.[3] Subheadings in this section include "Pregnancy Testing," "Contraception," and "Infertility."

Finally, the PLLR requires manufacturers to update all labels as new information or data become available.

Table 2 Comparison of Pregnancy and Lactation Labeling Rules: 1979 versus 2015[2,3]

Rule in Phase-Out	New PLLR
Pregnancy risk letter categories (A, B, C, D, X) assigned.	Pregnancy risk letter categories eliminated.
Section 8.1 Pregnancy Section 8.2 Labor and Delivery	Combined to form one section: 8.1 Pregnancy • Pregnancy Exposure Registry • Risk Summary • Clinical Considerations • Data
Section 8.3 Nursing Mothers	Becomes Section 8.2 Lactation • Risk Summary • Clinical Considerations • Data
Requirement to update the label as information becomes outdated	Requirement to update the label as information becomes outdated
–	New section added: 8.3 Females and Males of Reproductive Potential * • Pregnancy Testing • Contraception • Infertility

PLLR = Pregnancy and Lactation Labeling Rule.

* Only included when there are recommendations or requirements for pregnancy testing and/or contraception before, during, or after drug therapy, and/or there are human and/or animal data suggesting drug-associated effects on fertility and/or preimplantation loss effects.

IMPLEMENTATION OF THE PLLR

The PLLR became effective on June 30, 2015, and implementation of this rule will occur in several stages over three to five years from that date. Compliance will be determined by drug application and approval dates (Table 3).

The new rule has several potential limitations. Older medications and over-the-counter products approved prior to June 30, 2001, will have neither a pregnancy category nor a narrative summary readily available to providers. The requirement of close collaboration between the FDA and manufacturers to ensure timely updates also may be problematic.[8] In addition, consumers need to cooperate with the pregnancy registry process and share their health information in order to accumulate a meaningful quantity of data.[9]

LABELING SAMPLES

Since the effective date of the PLLR, a total of 48 new novel drugs have been approved by the FDA.[10,11] Only three of these (insulin degludec injection [Tresiba, Novo Nordisk], brivaracetam [Briviact, UCB, Inc.], and obiltoxaximab [Anthim, Elusys Therapeutics, Inc.]) have not yet conformed to the new rule.[12–14]

Elbasvir/grazoprevir (Zepatier, Merck), approved on January 28, 2016, is a good example of compliance with the PLLR.[15] Its section "8.1 Pregnancy" provides a narrative risk summary and detailed animal data, a background risk statement, and the estimated background risk for major birth defects and miscarriage. Section "8.2 Lactation" similarly summarizes risk and provides available animal data. Because there are no human pregnancy or lactation data for elbasvir/grazoprevir, only the animal data are summarized. Finally, per labeling guidelines, no pregnancy category is provided.

If the previous pregnancy category guidelines were to be applied to elbasvir/grazoprevir, a category of "B" may have been appropriate. However, this category would be overly simplistic and would not detail the animal data available for this agent. Therefore, in this case, a narrative as required for PLLR compliance presents useful information rather than a broad category or recommendation.

Trabectedin (Yondelis, Janssen Biotech), approved on October 23, 2015, also provides labeling that conforms to the PLLR and includes the new section "8.3 Females and Males of Reproductive Potential." The "Contraception" subheading provides specific contraception guidelines for women and men, while the "Infertility" subheading informs prescribers and

Table 3 Implementation Schedule of the New PLLR[2]

Applications for Drug or Biological Product	Compliance Requirements
Approved prior to June 30, 2001	Remove pregnancy category within 3 years of the effective date of PLLR. No other compliance requirements.
Approved June 30, 2001–June 29, 2002	3 years after the effective date of PLLR.
Approved June 30, 2002–June 29, 2005	5 years after the effective date of PLLR.
Approved June 30, 2005–June 29, 2007	3 years after the effective date of PLLR.
Approved June 30, 2007–June 30, 2015	4 years after the effective date of PLLR.
Pending approval on June 30, 2015	4 years after the effective date of PLLR or at time of approval, whichever is later.
Submitted on or after June 30, 2015	Time of submission.

PLLR = Pregnancy and Lactation Labeling Rule.

patients that Yondelis has the potential to decrease fertility in both genders.[16] The labeling information produced under the new rule allows the provider and patient to review and discuss the risks in order to make an informed treatment decision.

CLINICAL IMPACT

Although the PLLR requires a concise, standardized summary of available evidence, the departure from pregnancy categories may prove to be a challenging transition. The FDA received 16 comments regarding the proposed rule that supported the old category system. Those comments stated that the old system was simple and effective and expressed concern that a narrative summary may prove confusing and could lead to inconsistent decision-making.[2] The transition to a narrative summary style is not without risk and requires that providers review the available evidence instead of relying on category designations.[17] Such evidence review will require more time and may involve some complex decision-making. Risk arises if an incomplete assessment is made or if the evidence is unclear. The lack of a standardized schema may also make it difficult to make blanket formulary decisions because each medication will need a more individualized review.

CONCLUSION

In announcing the final PLLR, Sandra Kweder, MD, Deputy Director of the Office of New Drugs in the FDA's Center for Drug Evaluation and Research, stated, "Prescribing decisions during pregnancy and lactation are individualized and involve complex maternal, fetal, and infant risk–benefit considerations. The letter category system was overly simplistic and was misinterpreted as a grading system, which gave an oversimplified view of the product risk."[18] The PLLR remedies the perception of pregnancy categories as a grading system by doing away with them altogether. In place of pregnancy categories, the PLLR requires narrative explanations of risk and supporting data.

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