



Editorial

Understanding the new FDA pregnancy and lactation labeling rules[☆]

Dermatologists should be aware that the new Pregnancy and Lactation Labeling Rule (PLLR) has taken effect on June 30th, 2015. This mandate from the Federal Drug Administration (FDA) eliminated the standard pregnancy category letters for prescription medications (A, B, C, D and X). The new recommendations are now in the form of drug labeling that contains increased detail but also increased complexity. This editorial describes the new drug-labeling rule and its potential impact in clinical dermatology.

The PLLR introduced a new drug labeling schema to help physicians better communicate the risks and benefits of pharmacologic treatment to patients during pregnancy and lactation. Sandra Kweder, M.D., Deputy Director of the Office of New Drugs in the FDA's Center for Drug Evaluation and Research, stated, "The previous letter category system was overly simplistic and was misinterpreted as a grading system, which gave an over-simplified view of the product risk." (US Food and Drug Administration, 2015) Consequently, the new package insert content and formatting requirements aim to provide a more consistent way of disclosing relevant information about the risks and benefits of prescription drugs and biological products used during pregnancy and breastfeeding. However, some have expressed criticism of the PLLR. Many question how labels will be revised to reflect new data as it becomes available. Drug manufacturers face a significant challenge in condensing vast amounts of varying quality data into concise, clear paragraphs.

Despite these challenges, the rule immediately applies to all drugs approved by the FDA after June 30th 2015 and requires that all labels be continually updated as new information becomes available (US Food and Drug Administration, 2015). Pregnancy labels for products approved between 2001 and June 30th 2015 will be revised using a staggered implementation schedule, and those approved before 2001 must be revised within 3 years (US Food and Drug Administration, 2015). To aid in transition, the FDA issued draft guidance to assist drug manufacturers in complying with the new labeling content and format requirements (US Food and Drug Administration, 2015). Unfortunately, labels for over-the-counter medications are not affected by the PLLR.

The most notable change of the PLLR is that it will remove arbitrary and often misinterpreted pregnancy-labeling categories for pharmaceuticals (A, B, C, D, X). Instead, package inserts will now

contain individualized narrative summaries for each medication that includes the "risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation." (Food and Drug Administration, HHS, 2014).

This improved labeling schema is timely since nine out of ten women take at least one medication during pregnancy, and the use of four or more medications during pregnancy has doubled over the last 30 years (Mosley et al., 2015). Many pregnant women also suffer from chronic conditions such as asthma, high blood pressure, diabetes, mental illness, rheumatologic, and dermatologic disease that necessitate continued medical therapy during pregnancy and lactation.

The PLLR requires the use of three new subsections titled "Pregnancy," "Lactation" and "Females and Males of Reproductive Potential." This replaces the old schema (Fig. 1) that contained 3 distinct subsections that described "Pregnancy," "Labor and Delivery," and "Nursing Mothers." "Pregnancy" and "Labor and Delivery" have now been combined into "Pregnancy," and the old subsection of "Nursing Mothers" is now labeled "Lactation." In addition, a new subsection has been created to describe risks to "Females and Males of Reproductive Potential."

The "Pregnancy" subsection requires a previously recommended pregnancy exposure registry for drugs approved for use during pregnancy. It also contains a summary of the available data on any particular developmental outcome specific to gestational timing of exposure, which was previously not reported. The "Lactation" subsection provides additional information regarding the amount of drug transferred to breast milk and the specific potential effects on breastfed infants. Finally, the "Females and Males of Reproductive Potential" subsection discusses the need for pregnancy testing, contraception recommendations, and includes information about drug related infertility.

The PLLR has several promising implications for clinical practice. In place of an arbitrary lettering system, detailed risk summaries provide more comprehensive information derived from clinical experience (if any), animal data, and concerns related to the pharmacologic activity of the drug (Addis et al., 2000; Boothby and Doering, 2001; Doering et al., 2002). This information puts the potential effects of the drug into perspective to provide a more individualized risk-benefit analysis by patients and physicians. The new labeling system will also reduce the "innocent until proven guilty" bias, where untested drugs with no known harmful side effects were perceived to be safer (Category B) than tested drugs with known side effects (Category C) (Danesh and Murase, 2015).

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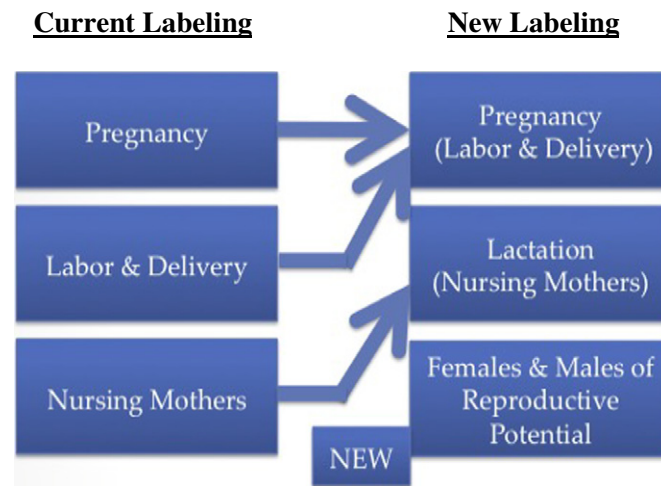


Fig. 1. Comparison of the current prescription drug labeling with the new PLLR labeling requirements.

Most of the currently available reproductive safety information on biologic drugs is derived from spontaneous reports or underpowered cohort studies, which contain inconsistent information that requires scrutiny when assessing outcomes (Calligaro et al., 2015). Postmarketing surveillance efforts have not been a priority for manufacturers in most cases, but the PLLR now requires pregnancy registries to become a routine part of postmarketing surveillance. This should provide adequate data to help physicians, pregnant patients, and breastfeeding mothers make complex healthcare decisions.

The PLLR also poses a number of challenges. The new system is more explicit about the sources of data on the label, and it is likely

to further expose that most pharmaceutical data relating to pregnancy is based on animal studies (92.9% from animal studies versus 5.2% from human pregnancy studies) (Mazer-Amirshahi et al., 2014; Chambers, 2014). The same can be said for breast-feeding labels. Data was not available on 47.9% of all labels; data for animals was only available on 42.7% of labels, and data for humans was only present on 4.7% of labels (Mazer-Amirshahi et al., 2014). The rule provides practitioners with more detailed information regarding pregnancy, lactation, and reproduction. It, therefore, places an increased responsibility on dermatologists to ensure that the paucity of available safety data is explained to their patients.

Sample step-by-step instructions for how to view the pregnancy, lactation, and male fertility data for sonidegib

1. Go to <http://dailymed.nlm.nih.gov/dailymed/index.cfm>
2. In the search box type sonidegib
3. Click on sonidegib
4. Scroll down and Click on Section 8: USE IN SPECIFIC POPULATIONS
5. Review data for trabectedin in section 8.1, 8.2, and 8.3
6. 8.1 Pregnancy
7. 8.2 Lactation
8. 8.3 Females and Males of Reproductive Potential

*A complete drug monograph for sonidegib for locally advanced basal cell carcinoma may be found at: <http://reference.medscape.com/drug/odomzo-sonidegib-1000039-6>

* A complete drug monograph for cobimetinib for advanced melanoma may be found at: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c387579e-cee0-4334-bd1e-73f93ac1bde6>

Fig. 2. Sample step-by-step instructions for how to view the pregnancy, lactation, and male fertility data for sonidegib.

Patients often desire more information than is currently provided (Edwards et al., 2002). Previously, physicians were able to use pregnancy categories as simple surrogates for risk stratification, with A being considered the safest and X the most dangerous (US Food and Drug Administration website, 1999). The new labels require physicians to not only read and understand the potential risks of a medication but also interpret literature that supports these risks. Physicians must then explain these risks in a clear concise manner to patients before a decision is made about starting a medication. The challenge of explaining probabilities to patients regarding risk is well known, and there is no universally accepted format for doing so (Danesh and Murase, 2015; Visschers et al., 2009). These obstacles will likely push physicians to develop new ways of coherently and efficiently engaging patients in making difficult decisions. To make the transition easier, "decision aids" that include visual presentations of risk information may be used to relate information to more familiar risks (Edwards et al., 2002). For example, some patients may prefer simple bar charts as opposed to a verbal explanation that explains risk versus benefits.

Despite these challenges, the PLLR presents an opportunity to improve patient care. It is well known that good communication is a requisite to good patient care and enhances the patient-physician relationship (Singh, 2015). The PLLR will motivate physicians to further develop their communication skills and better equip them to help patients make informed healthcare decisions. A helpful text for physicians with questions in this area is "Drugs in Pregnancy and Lactation" by Gerald G. Briggs (Briggs et al., 2012). All dermatologists and other physicians should familiarize themselves with the final PLLR guidelines available at <http://federalregister.gov/a/2014-28241>, and drug labels may be found at <http://dailymed.nlm.nih.gov/dailymed/index.cfm> (Fig. 2).

References

- Addis A, Sharabi S, Bonati M. Risk classification systems for drug use during pregnancy: are they a reliable source of information? *Drug Saf* 2000;23:245–53.
- Boothby LA, Doering PL. FDA labeling system for drugs in pregnancy. *Ann Pharmacother* 2001;35:1485–9.
- Briggs Gerald G, Freeman Roger K, Yaffe Sumner J. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Lippincott Williams & Wilkins; 2012.
- Calligaro A, Hoxha A, Ruffatti A, Punzi L. Are biological drugs safe in pregnancy? *Reumatismo* 2015;66(4):304–17.
- Chambers CD. Evaluating the impact of FDA's pregnancy and lactation labeling rule. *Dermatology News*; 2014 [Available at: <http://www.edermatologynews.com/views/single-view/evaluating-the-impact-of-fdas-pregnancy-and-lactation-labeling-rule/0c73d9cc718200951776403b0a9d8760.html>, Accessed September 9, 2015].
- Danesh MJ, Murase JE. The new US Food and Drug Administration pregnancy and lactation labeling rules: Their impact on clinical practice. *J Am Acad Dermatol* 2015; 73(2):310–1.
- Doering PL, Boothby LA, Cheek M. Review of pregnancy labeling of prescription drugs: is the current system adequate to inform of risks? *Am J Obstet Gynecol* 2002;187:333–9.
- Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. *Br Med J* 2002;324(7341):827–30.
- Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. *Fed Regist* 2014;79:72063–103.
- Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, van den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. *Am J Obstet Gynecol* 2014;211:690.e1–690.e11.
- Mosley II JF, Smith LL, Dezan MD. An overview of upcoming changes in pregnancy and lactation labeling information. *Pharm Pract (Granada)* 2015;13(2):605 [Epub 2015 Jun 15].
- Singh M. Communication as a Bridge to Build a Sound Doctor–Patient/Parent Relationship. *Indian J Pediatr* 2015 [Epub ahead of print].
- US Food and Drug Administration. FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products; 2015.
- US Food and Drug Administration website. Summary of comments from a public hearing and model pregnancy labeling based on recommendations. Available at: <http://www.fda.gov/ucsf/idm.oclc.org/ohrms/dockets/ac/99/transcript/3516r1.doc>; 1999. [Accessed September 9, 2015].
- Visschers VH, Meertens RM, Passchier WW, de Vries NN. Probability information in risk communication: a review of the research literature. *Risk Anal* 2009;29: 267–87.

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