

Drug Labeling Specialist on New Pregnancy Labeling Rules

Charles O. Jaap V, MBA, RAC

On June 30, 2015, the new pregnancy labeling rules for prescription drug labeling took effect,¹ marking the demise of pregnancy categories (A, B, C, D, X), in use since 1979.² The new rule ushers in what is expected to be an era of unprecedented inclusion with regard to descriptive risk and benefit information. According to FDA, “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”.³

This paper is written to provide a historical background on pregnancy labeling, to provide an overview of the new regulatory requirements, and to offer assistance in reformatting, rewriting pregnancy labeling in compliance with the new regulations. If your organization would benefit from professional consulting to ensure current, complete and compliant pregnancy labeling, information to that effect is available in the final paragraph of this paper.

Birth anomalies resulting from drug use during pregnancy became a prominent concern after the 1961 discovery of thalidomide induced malformations in newborns. By the end of the 1960s regulatory agencies in many countries had adopted or rewritten teratogenicity testing requirements. By the 1970s, prescribers were faced with increasing amounts of labeled preclinical, clinical and post-marketing data of varying quality, utility and presentation.⁴

Between the years preceding the implementation of the pregnancy categories (mid 1970s) and those preceding the pregnancy labeling rule of 2015, first-trimester use of prescription drugs worldwide increased over 60%. The use of *four* or more medications during pregnancy multiplied by over three-fold. It has also been reported that 1 in 6 women of childbearing age now use medications that may be teratogenic. Because approximately half of US pregnancies are unintended, the inadvertent and widespread fetal exposure to potential teratogens is inevitable.⁵

In 1975, FDA initiated a broad effort to improve the content and format of prescription drug labeling that continues today. Regulations were proposed that would standardize the types of information to appear under each of the labeling section headings^{6,7} and were finalized on December 26, 1979.⁸ A description of the resulting pregnancy subsections that resulted (under the old “Precautions” section of pre-Physician Labeling Rule [PLR] labeling) appear in Table 1. The then newly designated pregnancy categories are described in Table 2.

¹ Federal Register; Vol. 79, No. 233, Thursday, December 4, 2014

² Ibid

³ Ibid

⁴ Public Affairs Committee of the Teratology Society. Teratology Public Affairs Committee Position Paper: Pregnancy Labeling for Prescription Drugs: Ten Years Later. Birth Defects Research. 2007; 79:627-630

⁵ Parotti CO, Ng EW, Wyszynski DF. Contraception Methods in Drug Labeling. Drug Information Journal. 2012; 46: 320-328.

⁶ Federal Register; Vol. 40, No. 67, Monday, April 7, 1975

⁷ FDA Scraps Pregnancy Labeling Classification System in Favor of New Standard - <http://www.raps.org/Regulatory-Focus/News/2014/12/03/20893/FDA-Scraps-Pregnancy-Labeling-Classification-System-in-Favor-of-New-Standard/> Published December 3, 2014. Accessed June 19, 2015.

⁸ Federal Register; Vol. 44, No. 124, Tuesday, June 26, 1979

Table 1: Pregnancy Subsections (of Precautions Section) Resulting from 1979 Rule⁹

Pregnancy Subsection

Unless a drug was not absorbed systemically and was not known to have a potential for indirect harm to a fetus, a "Pregnancy" subsection must be included within the "Precautions" section of the labeling. The 1979 regulations required that the "Pregnancy" subsection contain information on the drug's teratogenic effects and other effects on reproduction and pregnancy and, when available, a description of human studies with the drug and data on its effects on later growth, development, and functional maturation of the child. The 1979 regulations also required that each product be classified under one of five pregnancy categories (A, B, C, D, or X) on the basis of risk of reproductive and developmental adverse effects or, for certain categories, on the basis of such risk weighed against potential benefit.

Labor and Delivery Subsection

Under certain circumstances, the labeling must include information on the effects of the drug on, among other things, the mother and the fetus, the duration of labor and delivery, and the effect of the drug on the later growth, development, and functional maturation of the child.

Nursing Mothers Subsection

With regard to labeling on lactation, the 1979 regulations required, at what was redesignated in 2006 as § 201.57(c)(9)(iii) and § 201.80(f)(8), that a "Nursing mothers" subsection be included in the "Precautions" section of the labeling. The "Nursing mothers" subsection provided that if a drug was absorbed systemically, the labeling must contain information about excretion of the drug in human milk and effects on the nursing infant, as well as a description of any pertinent adverse effects observed in animal offspring. The "Nursing Mothers" subsection required the use of certain standard statements depending on whether the drug was known to be excreted in human milk and whether it was associated with serious adverse reactions.

Table 2: Pregnancy Categories Resulting from 1979 Final Rule (Now Being Phased Out)¹⁰

Pregnancy Category A indicates that adequate and well controlled (AWC) studies in pregnant women have been conducted and these studies have failed to demonstrate fetal risk in the first trimester, and there is no evidence of fetal risk in later trimesters.

Pregnancy Category B indicates that animal studies have been performed. However, the animal studies either failed to demonstrate fetal risk (and there are no AWC studies in pregnant women); or the animal studies demonstrated fetal risk (and AWC studies in pregnant women have not been conducted *during the first trimester of pregnancy*, and there is no evidence of fetal risk in later trimesters).

Pregnancy Category C indicates that animal studies have been performed, and the studies have shown adverse effects on the fetus; or that animal studies have not been performed *and* there are no AWC studies in pregnant women. *However, the benefits of using the product in pregnant women may be acceptable despite the potential risks.*

⁹ Federal Register; Vol. 79, No. 233, Thursday, December 4, 2014

¹⁰ FDA Background Package For Meeting of Drug Safety and Risk Management Advisory Committee (DSaRM) Management of Drug Related Teratogenic Risk -Day One. December 12, 2012

Pregnancy Category D indicates that data from human investigations, marketing experience, or human studies have demonstrated evidence of fetal risk. *However, the potential benefits from using the drug in pregnant women may be acceptable despite its potential risks.*

Pregnancy Category X indicates that animal studies and human studies have demonstrated fetal abnormalities, or there is positive evidence of fetal risk based on data from human investigations, marketing experience, or studies, or both. *For products in this category, the risk to the fetus clearly outweighs any possible benefit to the use of the drug during pregnancy.*

Prior to the finalization of the 1979 rule, there was no specific language requirement concerning the use of drugs in women of child bearing potential. Rather, there were a multitude of general and non-standardized warnings. Citing “past experience with confusing and inconsistent labeling relating to use in pregnancy”, FDA proposed the pregnancy categories as we know them today^{11 12} in order to “standardize the presentation of experimental animal and human data on potential pregnancy effects of medications and to provide a risk-benefit formula for practitioners.”¹³

From the very beginning, the pregnancy categories faced criticism. One of the major areas of challenge voiced in response to the 1975 proposal was that the categories would be perceived as a measure of degrees of risk concerning drug use during pregnancy. In fact, FDA noted the same concern 37 years later in a document entitled Background Package For Meeting of Drug Safety and Risk Management Advisory Committee:

*From the time that the pregnancy categories were established, there has been concern that the pregnancy categories mislead healthcare professionals (and the women they counsel) to believe that the pregnancy categories reflect a scale of increasing risk (either in severity, frequency, or type) to the fetus. The misperception is that a drug product’s risk to the fetus progressively increases from Category A (perceived by many as the lowest) through categories B, C, and D, and ultimately to Category X (perceived by many as the highest risk). However, categories C, D, and X are not simply based on risk, but are assigned after consideration of risk balanced against benefit when used in pregnancy. Thus, a drug in categories C or D may have data suggesting a similar teratogenic risk as a drug in Category X, but the assignment of the pregnancy category varies because of a different risk/benefit balance. Additionally, the categories themselves do not always distinguish between risks that are based on human versus animal data findings, or between differences in frequency, severity, and type of fetal developmental toxicities.*¹⁴

In 1992, the Public Affairs Committee of the Teratology Society sponsored a symposium on pregnancy categories (Friedman, 1993). One of the major concerns expressed was that “the alarmist features of this system led to unnecessary termination of wanted pregnancies”.¹⁵ In 1994, the same committee published a position paper entitled FDA Classification of Drugs for Teratogenic Risk, which recommended the FDA “Use-In-Pregnancy ratings be deleted from drug labeling and replaced by

¹¹ Federal Register; Vol. 40, No. 67, Monday, April 7, 1975

¹² Corbett K, Kremzner M, Stifano T. Providing adequate directions for medication use in pregnant women and nursing mothers: An overview of pregnancy labeling. American Academy of Nurse Practitioners. 2011; 23:389-391

¹³ Public Affairs Committee of the Teratology Society. Teratology Public Affairs Committee Position Paper: Pregnancy Labeling for Prescription Drugs: Ten Years Later. Birth Defects Research. 2007; 79:627-630

¹⁴ FDA Background Package For Meeting of Drug Safety and Risk Management Advisory Committee (DSaRM) Management of Drug Related Teratogenic Risk -Day One. December 12, 2012

¹⁵ Public Affairs Committee of the Teratology Society. Teratology Public Affairs Committee Position Paper: Pregnancy Labeling for Prescription Drugs: Ten Years Later. Birth Defects Research. 2007; 79:627-630

narrative statements that summarize and interpret available data regarding hazards of developmental toxicity and provide estimates of teratogenic risk" (Public Affairs Committee, 1994)." ¹⁶

Faced with mounting pressure, in 1997 FDA conducted a Public Hearing to begin the process of reevaluating the utility and value of the pregnancy categories. ^{17 18} Two years later, in 1999 FDA conducted two focus groups that included obstetrician-gynecologists and family practitioners at the 15th Annual Clinical Update in Obstetrics and Gynecology Conference. ¹⁹ Also that year, the Subcommittee of the Advisory Committee for Reproductive Health Drugs met to discuss possible changes to pregnancy labeling, as well as the development of various draft guidance documents and risk communications. ²⁰ At that meeting, model labeling format based on earlier proceedings was presented as a Concept Paper on Pregnancy Labeling. ^{21 22} A chronology of major regulatory events associated with the pregnancy labeling rule-making process is presented in Table 3.

Table 3: Chronology of Major Regulatory Events Leading to the 2015 Final Pregnancy Labeling Rule

April 7, 1975 – FDA announces initiative to improve the content and format of prescription drug labeling ²³

June 26, 1979 – The rule is finalized. ²⁴ Pregnancy subsection, Pregnancy Categories, Labor & Delivery subsection, and Nursing Mothers subsection are born.

December 26, 1979 – effective date of the final rule. ²⁵

September 12, 1997 – Public Hearing focuses on the requirement that each drug product be classified into one of five pregnancy categories. ^{26 27}

February 1999 – FDA conducts two focus groups that include obstetrician-gynecologists and family practitioners at the 15th Annual Clinical Update in Obstetrics and Gynecology Conference. ²⁸

June 3, 1999 – Subcommittee of the Advisory Committee for Reproductive Health Drugs discusses possible changes to pregnancy labeling as a result of the 1997 public hearing, as well as the development of various draft guidance documents and risk communications. ^{29 30}

¹⁶ Ibid

¹⁷ Federal Register; Vol. 62, No. 147, Thursday, July 31, 1997

¹⁸ Federal Register; Vol. 64, No. 83, Friday, April 30, 1999

¹⁹ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

²⁰ Federal Register; Vol. 64, No. 83, Friday, April 30, 1999

²¹ Concept Paper on Pregnancy Labeling. Summary of Comments from a Public Hearing and Model Pregnancy Labeling Based on Recommendations. May 20, 1999

²² Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

²³ Federal Register; Vol. 40, No. 67, Monday, April 7, 1975

²⁴ Federal Register; Vol. 44, No. 124, Tuesday, June 26, 1979

²⁵ Ibid

²⁶ Federal Register; Vol. 62, No. 147, Thursday, July 31, 1997

²⁷ Federal Register; Vol. 64, No. 83, Friday, April 30, 1999

²⁸ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

²⁹ Federal Register; Vol. 64, No. 83, Friday, April 30, 1999

³⁰ Federal Register; Vol. 64, No. 83, Friday, April 30, 1999

May 2000 - FDA conducts four more focus groups to evaluate standard statements under consideration.³¹

September 12, 2000 – Joint Meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee with the Pregnancy Labeling Subcommittee of the Advisory Committee for Reproductive Health Drugs discusses lactation issues.^{32 33}

January 25, 2006 - Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (aka Physician's Labeling Rule or PLR) becomes a final rule.³⁴

June 30, 2006 – PLR effective date.

May 29, 2008 – The pregnancy labeling rules are proposed: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling.³⁵

December 4, 2014 – Pregnancy labeling rule is final.³⁶

June 30, 2015 – Effective date of Final Rule.³⁷

In 2000, FDA conducted four more focus groups to evaluate standard statements under consideration. Two groups consisted of nurse-midwives attending the annual meeting of the American College of Nurse-Midwives and the other two included obstetrician/gynecologists attending the annual meeting of the American College of Obstetricians and Gynecologists.³⁸ Once again that year, another Advisory Committee meeting was convened (Joint Meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee With the Pregnancy Labeling Subcommittee of the Advisory Committee for Reproductive Health Drugs) to discuss lactation issues.^{39 40}

It should be noted that while the pregnancy categories were the subject of much criticism, the new pregnancy labeling requirements of 1979 did represent improvement. For example, Phenergan® (promethazine), an antihistamine with multiple indications had no pregnancy information in the labeling in 1979. By 1983, Phenergan was designated Pregnancy Category C and included a description of animal data in promethazine as well as other antihistamines (1978-1985 Physician Desk Reference). Dilantin® (phenytoin), an antiepileptic ultimately evolved from a 1978 label that stated "Usage in Pregnancy: The effects of Dilantin in human pregnancy and nursing infants are unknown..." to Pregnancy Category D and enrollment in a pregnancy registry (Drugs@FDA).

By 2006, the Physicians' Labeling Rule (PLR) was finalized.⁴¹ The requirements for the format and content of prescription drug labeling were significantly changed. Implementation requirements for

³¹ Ibid

³² Federal Register; Vol. 65, No. 163, Tuesday, August 22, 2000

³³ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

³⁴ Federal Register; Vol. 71, No. 15, Tuesday, January 24, 2006

³⁵ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

³⁶ Federal Register; Vol. 79, No. 233, Thursday, December 4, 2014

³⁷ Ibid

³⁸ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

³⁹ Federal Register; Vol. 65, No. 163, Tuesday, August 22, 2000

⁴⁰ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

⁴¹ Federal Register; Vol. 71, No. 15, Tuesday, January 24, 2006

submission of supplements were on a 'sliding scale' of dates that ranged from June 30, 2009 for "Applications pending on June 30, 2006 and applications approved 0 to 1 year before June 30, 2006" to June 30, 2013 for "Applications approved 4 to 5 years before June 30, 2006". Applications approved over five years prior to June 30, 2006 were allowed to submit supplements voluntarily at any time. It should be noted that the regulations were shifted such that PLR labeling format is now described in 21 CFR 201.57, whereas the previous era labeling (at one time occupying 201.57) is now described in 21 CFR 201.80.

At that time, the pregnancy revisions were still the subject of a separate rulemaking process, and were not ready in time for PLR placement. However, the "Precautions" section of labeling was eliminated by the PLR. Because of such factors, the new labeling requirements did not include changes to the pregnancy subsections, although they were relocated from the "Precautions" section to "Use in Specific Populations" section.⁴²

On May 29, 2008, the pregnancy labeling rule was proposed with the purpose of amending the regulations that govern the content and format of the "Pregnancy," "Labor and delivery," and "Nursing Mothers" subsections of the "Use in Specific Populations" section of PLR labeling and the "Precautions" section of non-PLR labeling for human prescription drug and biological products. The new subsections were proposed to be entitled "Pregnancy", "Lactation", and "Females and Males of Reproductive Potential". When finalized in 2014, the Agency noted that many of the provisions in the Proposed Rule were included in the Final Rule,⁴³ and indeed the subsections were named as proposed. Following are summary descriptions of the new 2015 subsections.

Pregnancy

The new rule merges the previous Pregnancy and Labor and Delivery subsections into a single "Pregnancy" subsection and requires the removal of the pregnancy categories (A, B, C, D, and X) from all drug product labeling. This subsection must also include a narrative "Risk Summary". If the drug is absorbed systemically, the Risk Summary must include "risk statements based on data from all relevant sources (human, animal, and/or pharmacologic), that describe, for the drug, the risk of adverse developmental outcomes " and describe the data that are the basis for the statements and clinical information.

Because FDA wishes to improve data collection and encourage participation in pregnancy exposure registries, if the drug is subject to a clinically relevant registry, the subsection must include a statement to that effect. Contact and enrollment information must also be included. The Agency has also expressed a desire to support prescribers understanding of risks and benefits, facilitate informed prescribing decisions and improve patient counseling. Thus, the subsection must also contain information such as "disease-associated maternal and/or embryo/fetal risk, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery".

Lactation

This new subsection requires a summary of the risks of using a drug during lactation as well as information about the data forming the basis for the included risk summary and clinical information. The

⁴² Public Affairs Committee of the Teratology Society. Teratology Public Affairs Committee Position Paper: Pregnancy Labeling for Prescription Drugs: Ten Years Later. Birth Defects Research. 2007; 79:627-630

⁴³ Federal Register; Vol. 73, No. 104, Thursday, May 29, 2008

risk summary must include, to the extent it is available, relevant information on the presence of the drug in human milk, effects of the drug on the breast-fed child, and effects of the drug on milk production. At the end of the summary of risks, a risk and benefit statement must also appear (unless breastfeeding is contraindicated during drug therapy). Further, information on minimizing drug exposure in breast-fed children (in certain situations) and available interventions for monitoring or mitigating the adverse reactions presented in other sections of the labeling must be presented.

Females and Males of Reproductive Potential

Because there has been no consistent labeling of pregnancy testing, contraception, or infertility information, the "Females and Males of Reproductive Potential" will now be required to do so. The subsection will also note whether such prophylactic measures are required/recommended before, during, or after drug therapy as well and describe human or animal data that suggest drug-associated fertility effects.

Not surprisingly, implementation of the new rule will be phased in over the coming years. This is illustrated in Table 4. Applications not subject to the requirements of the PLR (NDA, BLA, or efficacy supplements) approved before June 30, 2001 must remove the pregnancy category from their labeling within 3 years after the effective date of the rule (June 30, 2015). Those applications approved on or after June 30, 2001 (and therefore subject to PLR) are subject to a phased-in implementation plan that would stagger the required dates these products would be required to replace the content and formatting of the pregnancy and lactation subsections of their labeling with the new content and required formatting.⁴⁴

Table 4: Implementation of the 2015 Pregnancy Labeling Rule

Applications required to conform to new pregnancy/lactation content requirements	Time by which labeling with new Pregnancy/lactation content must be submitted to FDA for approval
New or Pending Applications	
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
Approved Applications Subject to the Physician Labeling Rule	
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

⁴⁴ Federal Register; Vol. 79, No. 233, Thursday, December 4, 2014

The new pregnancy labeling rule poses the challenge of reformatting, correcting or deleting obsolete information, writing new material, and ensuring complete, current, comprehensive and compliant information. One of the keys to success is the effective deployment of pharmacovigilance, scientific writing, labeling, and regulatory affairs expertise and resources.

For 30+ years, PDG's senior consultants and scientists have garnered considerable experience in the amplification of safety related information within pregnancy labeling. This experience derives from the design, conduct, and interpretation of pre-clinical and clinical studies to investigate the efficacy and safety of various drug products for regulatory approvals. Additionally, PDG possesses extensive experience in pharmacovigilance activities to assess the risks and benefits associated with drug products. This includes the monitoring and evaluation of all sources of adverse events and the design and conduct of follow-up studies to discern newly identified events or changes in frequency or severity of already identified events.

PDG's scientific writers are also adept at timely communication of new safety information through media such as Dear Healthcare Professional letters, integrated summaries, press releases, and other publications to promptly and accurately alert prescribers, patients, and FDA to newly labeled information. Please feel free to [contact us](#).

Charles Jaap is Vice-President of Operations and Business Development for Pharmaceutical Development Group, Inc. (PDG). PDG is a global pharmaceutical consultant with extensive experience in the strategic development of 505(b)(2) drug products. From identification and choice of viable candidates through ensuring the existence of cost-effective commercialization strategies, PDG is unique in its ability to comprehensively and ideally integrate products, dosage forms, populations and FDA regulatory pathways. The opinions and statements in this paper are solely those of Charles Jaap and do not necessarily reflect those of PDG™.