Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact Rosemary Addy (CDER) at 301-796-2200, or Office of Communication, Outreach and Development (CBER) at 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)

December 2014
Labeling

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants in complying with new content and format requirements of the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling for human prescription drug and biological products[2] (as described in the final rule[3] published concurrently with this draft guidance). The guidance provides information for preparing subsections 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential of the USE IN SPECIFIC POPULATIONS section of the full prescribing information (FPI) described in 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii).

This guidance provides recommendations to applicants submitting new drug applications (NDAs), efficacy supplements to approved NDAs, biologics license applications (BLAs) (for biological products that are regulated as drugs), and efficacy supplements to BLAs as described in greater detail in the final rule and this draft guidance (as well as to applicants that have previously submitted such applications during the time periods specified in the implementation plan at Appendix B).

[1] This guidance has been prepared by the Division of Pediatric and Maternal Health in the Office of New Drugs in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

[2] This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug* or *drug product* will be used to refer to human prescription drug and biological products that are regulated as drugs.

[3] Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription drug labeling is a communication tool. Its principal objective is to make available to health care providers the detailed prescribing information necessary for the safe and effective use of a drug, and to do so in a manner that is clear and useful to providers when prescribing for and counseling their patients. Prescribing decisions during pregnancy and lactation are highly individualized and involve complex maternal, fetal, and infant risk–benefit considerations.

Concurrently with this draft guidance, FDA is publishing the final rule: *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, or final rule). The final rule provides a framework for clearly communicating information on the benefits and risks of using a drug during pregnancy and lactation to help facilitate prescribing decisions. The final rule also includes a subsection on Females and Males of Reproductive Potential to address issues in these populations that are linked to pregnancy either directly or indirectly (see explanation below).

The requirements on content and format of labeling for human prescription drug and biological products were revised by the January 24, 2006[4] final rule, commonly referred to as the Physician Labeling Rule (PLR). PLR labeling requirements are described in 21 CFR 201.56 and 201.57.

The PLLR revises the PLR content and format requirements for subsections 8.1 through 8.3 of section 8 USE IN SPECIFIC POPULATIONS of the FPI [21 CFR 201.57(c)(9)(i) through (c)(9)(iii)],[5] as follows:

8.1 Pregnancy

This subsection contains information on pregnancy, including labor and delivery. The final rule eliminates the **Labor and delivery** subsection because information about labor and delivery is included in the **Pregnancy** subsection of labeling.

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[4] See the final rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the *Federal Register* (71 FR 3922; January 24, 2006).

[5] 21 CFR 201.80 applies to products that are not required to convert their labeling to the PLR format. Under the final rule, products subject to § 201.80 only are required to remove the pregnancy letter category from their labeling (e.g., "Pregnancy Category C"), and not the standard statements that follow each of the pregnancy letter categories (e.g., "(Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."(21 CFR 201.80(f)(6)(i)(c)). Accordingly, the final rule also revises 21 CFR 201.80 by removing the references to the pregnancy letter categories in § 201.80(f)(6)(i)(a)-(e).

The final rule also removes the pregnancy categories (A, B, C, D, and X), which FDA determined were often confusing and did not accurately or consistently communicate differences in degrees of fetal risk. Because risk–benefit decisions regarding use of a drug during pregnancy are more complex than the category designations suggest, reliance on the categories by health care providers may often be misplaced and could result in poorly informed clinical decision making. Instead, under the final rule, narrative summaries of the risks of a drug during pregnancy and discussions of the data supporting those summaries are required in labeling to provide more meaningful information for clinicians.

8.2 Lactation

This subsection replaces **Nursing mothers**.

8.3 Females and Males of Reproductive Potential

This new subsection provides information on pregnancy testing, contraception, and infertility.

Historically, information about contraception and pregnancy testing recommendations that was directed toward the care of females and males of reproductive potential might be found in the **Pregnancy** subsection or in the WARNINGS AND PRECAUTIONS section of labeling. In contrast, clinical advice on infertility might be found with the animal data, in the ADVERSE REACTIONS section, or in the WARNINGS AND PRECAUTIONS section. This variability made it challenging for health care providers to locate and use the relevant and available information when prescribing for and counseling patients. The new subsection created under the final rule, **Females and Males of Reproductive Potential**, provides a dedicated subsection for pregnancy testing, contraception, and infertility information when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest drug-associated fertility effects.

III. GENERAL PRINCIPLES

A. Revising Labeling

Under 21 CFR 201.56(a)(2), "the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading." Consistent with this requirement, when revising existing labeling to comply with the PLLR regulations, applicants should evaluate labeling content to ensure that it accurately reflects current knowledge. Because most human pregnancy exposure and lactation data are collected in the postmarket setting, PLLR implementation provides an opportunity to evaluate available information and revise labeling accordingly. In addition, applicants will typically need to develop new content for certain subheadings, for example, the background rates of birth defects and miscarriage (see section IV.A below). Subsequent to the initial implementation of the pregnancy and lactation labeling changes required under the PLLR, and the requirements for the **Females and Males of Reproductive Potential** subsection, applicants must update labeling, consistent with § 201.56(a)(2).

B. Formatting

Subsection numbers and titles in the FPI must be bolded (e.g., **8.1 Pregnancy**) (§ 201.57(d)(7)). In addition, unique to the PLLR is the requirement for the inclusion of specific subheadings and headings under subheadings within subsections (e.g., Risk Summary). Subheading titles within these subsections should be italicized and/or underlined, and heading titles should be either italicized or underlined, and the approach used should be consistent throughout the labeling. Additional subdivisions of information other than those presented in Appendix A are not recommended.

C. Cross-Referencing

Cross-referencing follows the general principles of the PLR. In most situations, the PLLR subsections of labeling will contain the detailed and most important information relevant to prescribing in the patient populations at issue. Other sections of labeling (e.g., CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS) may briefly present a topic addressed in the PLLR subsections and will cross-reference the more detailed discussion(s) in the PLLR subsections. For example, if a clinically significant drug-associated adverse developmental outcome warrants a contraindication in pregnancy, the CONTRAINDICATIONS section will list pregnancy as a contraindication with a brief description of the observed or anticipated consequences of using the drug during pregnancy and will cross-reference to USE IN SPECIFIC POPULATIONS (8.1) for details.[6]

Because the PLLR requires the inclusion of specific subheadings within subsections (e.g., Risk Summary), cross-referencing within a subsection is often necessary. The recommended method of within-subsection cross-referencing is to present the title of the subheading being referenced in parentheses and italics (e.g., (*see Data*)).

IV. SPECIFIC SUBSECTIONS

A. 8.1 Pregnancy

Information in the **Pregnancy** subsection of labeling is presented under the following subheadings:

- Pregnancy Exposure Registry
- Risk Summary
- Clinical Considerations

[6] For information on how to determine when information related to a PLLR subsection warrants inclusion in the major safety sections of labeling, see FDA's guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format*.

FDA guidances are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The most recent version of a guidance can be obtained from this location.

- Data

For the purposes of the PLLR and this guidance, the term *drug* or *drug product* is used to refer to human prescription drug and biological products that are regulated as drugs. Because some drugs are prodrugs that are metabolized to an active form, it is assumed that human pregnancy data on any form of the drug (drug, prodrug, or active metabolite) is applicable in terms of developmental toxicity risk.

1. Pregnancy Exposure Registry

The purpose of including information on a scientifically acceptable pregnancy exposure registry in the **Pregnancy** subsection is to inform health care providers of the availability of a pregnancy exposure registry for a product. FDA believes that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving their usefulness. The Agency considers a pregnancy exposure registry scientifically acceptable when it is consistent with FDA guidance.[7]

If there is a scientifically acceptable pregnancy exposure registry for the drug, the following statement must appear under the subheading Pregnancy Exposure Registry (§ 201.57(c)(9)(i)(A)):

> "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy."

This statement must be followed by contact information (e.g., a toll-free telephone number, web site) needed to enroll in or to obtain information about the registry (§ 201.57(c)(9)(i)(A)).

When there is no pregnancy exposure registry, this subheading should be omitted.

The availability of a pregnancy exposure registry should be noted in the PATIENT COUNSELING INFORMATION section, and a cross-reference should be included to **8.1 Pregnancy** for the contact information necessary to enroll.

2. Risk Summary

The Risk Summary subheading is always required because certain statements are required to be included even when there are no data or information available. The Risk Summary provides "risk statement(s)" that describe for the drug, the risk of adverse developmental outcomes based on all relevant human data, animal data, and the drug's pharmacology (§ 201.57(c)(9)(i)(B)).

Adverse developmental outcomes include the following four groups of developmental toxicities[8]:

[7] See FDA's guidance for industry, *Establishing Pregnancy Exposure Registries*.

[8] See FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns*.

- "Structural abnormalities" describes dysmorphology, which includes malformations, variations, deformations, and disruptions
- "Embryo-fetal and/or infant mortality" describes developmental mortality, which includes miscarriage, stillbirth, and infant death (including neonatal death)
- "Functional impairment" describes functional toxicity, which includes such outcomes as deafness, endocrinopathy, neurodevelopmental effects, and impairment of reproduction
- "Alterations to growth" describes such outcomes as growth restriction, excessive growth, and delayed and early maturations

When multiple data sources are available, risk statements must be presented in the following order: human, animal, and pharmacologic (§ 201.57(c)(9)(i)(B)). The Risk Summary should be presented as an integrated summary, and not as an individualized listing of information. In some cases, multiple risk statements may be needed to address the risk for various outcomes. If there is more than one risk based on human data, the information should be placed in the order of clinical importance. The risk statement(s) based on animal data may differ from the risk statement(s) based on human data.

When applicable, risk statements must include a cross-reference to additional details in the relevant portion of the Data subheading in the **Pregnancy** subsection (§ 201.57(c)(9)(i)(B)).

If a drug is systemically absorbed, the Risk Summary must include information about the background risk of major birth defects and miscarriage in the U.S. general population, regardless of drug exposure (§ 201.57(c)(9)(i)(B)), in order to establish a basis for comparison. The most reliable, stable U.S. data on the prevalence of birth defects come from the Centers for Disease Control and Prevention (CDC) birth defects surveillance programs, and the rates for miscarriage are based on published data. At the time this guidance was published, review of available data suggested that major birth defects occur in 2-4% of the general population[9] and that miscarriage occurs in 15-20% of clinically recognized pregnancies.[10] If an applicant wishes to rely on different percentage ranges for these rates, the applicant should provide the justification for those figures in its application or labeling supplement. If information on birth defects and miscarriage is available for the patient population for whom the drug is labeled, it also must be included (§ 201.57(c)(9)(i)(B)). Applicants should periodically review the birth defects and miscarriage data to ensure that the information in labeling is accurate (see § 201.56(a)(2)).

When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary (§ 201.57(c)(9)(i)(B)). A brief description of the observed or anticipated consequences should also be included.

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[9] Rynn L, Cragan J, Correa A. Update on Overall Prevalence of Major Birth Defects-Atlanta, Georgia, 1978-2005. CDC MMWR January 11, 2008/57(01);1-5.

[10] American College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy; 2011.

If data demonstrate that a drug is not systemically absorbed following a particular route of administration, the Risk Summary must contain only the following statement (§ 201.57(c)(9)(i)(B)):

> "(Name of drug) is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug."

For situations in which the drug is not absorbed systemically following one route of administration, but the drug is absorbed systemically following another route (or other routes) of administration, the above statement should be included for the route of administration resulting in no systemic exposure. This would be in addition to any statements that are required in the Risk Summary based on data demonstrating that the drug is absorbed systemically following another route (or other routes) of administration.

The following discussion describes the requirements for the risk statements.

a. Risk statement based on human data

Determining whether pregnancy exposure data can establish a drug associated risk is a complex process that requires an assessment of the quality and quantity of available data.[11] Human data may come from any of the following sources, depending on the particular study design:

- Clinical trials
- Pregnancy exposure registries
- Other large scale epidemiologic studies

A well-documented case series may also support a statement about fetal risk in particular situations, such as detection of a structural abnormality that is rare in the general population, but occurs with relatively high frequency among exposed fetuses and infants.

When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, a risk statement based on human data must summarize the specific developmental outcome(s), and include the following information (§ 201.57(c)(9)(i)(B)(1)):

- Its incidence
- The effect of dose
- The effect of duration of exposure
- The effect of gestational timing of exposure

If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, this risk must be quantitatively compared to the risk for the same outcome in infants born to women who were not

[11] See FDA's reviewer guidance, *Evaluating the Risks of Drug Exposure in Human Pregnancies*.

exposed to the drug, but who have the disease or condition for which the drug is indicated to be used (§ 201.57(c)(9)(i)(B)(1)). When risk information is not available for women with these condition(s), the risk for the specific outcome in women exposed to the drug during pregnancy must be compared to the rate at which the outcome occurs in the general population (§ 201.57(c)(9)(i)(B)(1)).

When there are no human data or the available human data do not establish the presence or absence of drug-associated risk, this must be stated in the Risk Summary (§ 201.57(c)(9)(i)(B)(1)).

For vaccines,[12] consideration should be given to any risk to the fetus due to the vaccine active ingredient(s) or due to the maternal immune response to the active ingredient. For example, for live attenuated viral vaccines it may not be known whether the attenuated vaccine virus causes fetal harm when administered to a pregnant woman. However, naturally occurring virus infection may cause harm (e.g. rubella) thus, pregnant women may be advised to avoid vaccination during pregnancy.

b. Risk statement based on animal data

When animal data are available, the risk statement based on such data must describe the potential risk for adverse developmental outcomes in humans and summarize the available data (§ 201.57(c)(9)(i)(B)(2)).[13] This statement must include (§ 201.57(c)(9)(i)(B)(2)):

- The number and type(s) of species affected
- Timing of exposure
- Animal doses expressed in terms of human dose or exposure equivalents
- Outcomes for pregnant animals and offspring

The risk statement must state when animal studies do not meet current standards[13,14] for nonclinical developmental toxicity studies, or when there are no animal data (§ 201.57(c)(9)(i)(B)(2)).

Toxic drug exposure may manifest as one type of developmental effect (e.g., embryo-lethality) in an animal species, but a different type of developmental effect (e.g., structural abnormality) in humans. Therefore, FDA does not believe it is possible to conclude that a drug causes an increased risk of a particular type of developmental effect based on animal data alone. However,

[12] In this guidance, the term *vaccine* refers to preventive and therapeutic vaccines for infectious disease indications.

[13] See FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns.* For vaccines, see FDA's guidance for industry, *Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications.*

[14] For a description of current standards for nonclinical developmental toxicity studies, see FDA's guidance for industry, *M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and the International Conference on Harmonisation S5 (R2) Guideline: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility*.

an adverse developmental outcome is more concerning when the outcome occurs in more than one animal species, especially if the outcome is consistent across species.[15]

c. Risk statement based on pharmacology

When the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks (§ 201.57(c)(9)(i)(B)(3)). In addition, the Risk Summary should explain the mechanism of action and the potential associated risks when there is a well-understood pharmacologic mechanism of action that may result in drug class-associated adverse developmental outcomes. Examples of well-characterized biochemical and physiologic modes of action include cytotoxic drugs and drugs that inhibit normal sex hormone production. For other drugs, the concern may be based on biologic plausibility or human experience (e.g., drugs that interfere with DNA replication, induce cell death, or alter transmission in major neurotransmitter systems). A cross-reference should be provided to CLINICAL PHARMACOLOGY, where the pharmacologic data on which this Risk Summary is based are more fully described.

3. Clinical Considerations

The Clinical Considerations subheading (§ 201.57(c)(9)(i)(C)) provides information to further inform prescribing and risk-benefit counseling. Relevant information under the Clinical Considerations subheading is presented under the following five headings, to the extent it is available:

- Disease-associated maternal and/or embryo/fetal risk
- Dose adjustments during pregnancy and the postpartum period
- Maternal adverse reactions
- Fetal/Neonatal adverse reactions
- Labor or delivery

Headings should be omitted if there are no data to inform them or the available data are not informative. The Clinical Considerations subheading should be omitted in its entirety if all of the headings are omitted.

a. Disease-associated maternal and/or embryo/fetal risk

When relevant data are available, this portion of labeling must describe any serious known or potential risk to the pregnant woman and/or the embryo/fetus associated with the disease or condition for which the drug is indicated (§ 201.57(c)(9)(i)(C)(1)). This description is included to provide information on any serious risks of the untreated disease/condition in pregnancy, so that health care providers and patients may make informed decisions about treatment.

[15] See FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns*.

An example of a disease with serious risks unique to the pregnant woman and fetus is diabetes. Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and delivery complications due to fetal macrosomia (e.g., perineal injury and lacerations, need for cesarean section, and post-partum hemorrhage). Poorly controlled diabetes increases the fetal risk for neural tube defects, cardiovascular malformations, oral clefts, still birth, macrosomia related morbidity (e.g., brachial plexus injury, hypoxia), and neonatal hyperglycemia. Please note that FDA may consider developing class labeling for known maternal and/or embryo/fetal risks.

b. Dose adjustments during pregnancy and the postpartum period

If there are pharmacokinetic data that support dose adjustment(s) during pregnancy and the postpartum period, a summary of this information must be provided (§ 201.57(c)(9)(i)(C)(2)). As appropriate, additional information elsewhere in the labeling (e.g., CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION) should be cross-referenced.

Other relevant information may be included in labeling based on known effects of pregnancy on various cytochrome P450 enzymes and the known metabolic pathways of the drug. For example, it is well established that during pregnancy CYP1A2 activity decreases and CYP2D6 activity increases.[16,17] If a drug is primarily metabolized via a specific cytochrome P450 enzyme with well-documented activity changes in pregnancy, this subsection should include this information and inform the prescriber that this change may affect serum drug levels in the pregnant woman.

For vaccines, dose adjustments are not made based on pharmacokinetic data. Therefore, this heading is not applicable to vaccines.

c. Maternal adverse reactions

Labeling must describe drug-associated adverse reactions that are unique to pregnancy or occur with increased frequency or severity in pregnant women (§ 201.57(c)(9)(i)(C)(3)). If clinical interventions are available to help monitor or mitigate drug-associated maternal adverse reactions, these interventions must be described in this portion of labeling (§ 201.57(c)(9)(i)(C)(3)) (e.g., monitoring blood glucose for a drug that causes hyperglycemia in pregnancy). If known, the effect of dose, timing, and duration of exposure on the maternal risk of these adverse reaction(s) must be included (§ 201.57(c)(9)(i)(C)(3)).

d. Fetal/Neonatal adverse reactions

This heading describes fetal/neonatal adverse reactions that are not adverse developmental outcomes and that are not described in the Risk Summary. If it is known or anticipated that

[16] Tracy TS et al. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005 Feb; 192 (2):633-9.

[17] Anderson GD. Pregnancy-Induced changes in pharmacokinetics. Clin Pharmacokinet 2005; 44 (10):989-1008.

maternal drug therapy increases or may increase the risk of an adverse reaction in the fetus or neonate, based on the drug's pharmacologic activity, or other data, the labeling must describe the adverse reaction (§ 201.57(c)(9)(i)(C)(4)). The labeling must also describe the potential severity and reversibility of the adverse reaction and available intervention(s) for monitoring or mitigating the reaction in the fetus or neonate (§ 201.57(c)(9)(i)(C)(4)). If known, the effect of dose, timing, and duration of exposure on the risk must be included (§ 201.57(c)(9)(i)(C)(4)).

For example, opiates administered during labor for intrapartum analgesia may cause reversible respiratory depression in the neonate. Administration of naloxone is an available intervention for mitigating this reaction. Under the Fetal/Neonatal adverse reactions heading, the opiate labeling should describe this reaction and the available intervention.

e. Labor or delivery

If the drug is expected to affect labor or delivery, the labeling must provide available information about the drug's effects on the mother and the fetus or neonate, and the duration of labor and delivery (§ 201.57(c)(9)(i)(C)(5)). The labeling must describe any increased risk of adverse reactions, including their potential severity and reversibility, and available intervention(s) that can mitigate these effects and/or adverse reactions (§ 201.57(c)(9)(i)(C)(5)).

For drugs approved for use only during labor and delivery, this heading (and the information required under this heading) may be omitted (§ 201.57(c)(9)(i)(C)(5)).

4. Data

Under the subheading Data, labeling must describe the data that provide the scientific basis for the information presented in the Risk Summary and Clinical Considerations (§ 201.57(c)(9)(i)(D)(1)). This subheading is required, as are the headings Human Data and Animal Data, to the extent information is available. Human data and animal data must be presented separately, and human data must be presented first (§ 201.57(c)(9)(i)(D)(2)).

a. Human data

This portion of labeling describes the data supporting any risk statement(s) in the Risk Summary and the information under Clinical Considerations that is based on human data. Both positive and negative study findings must be included (§ 201.57(c)(9)(i)(D)(3)). Applicants must update labeling as new data become available (§ 201.56(a)(2)). Applicants should evaluate the quality and quantity of data available with respect to what information warrants inclusion in labeling.[18] This portion of labeling must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects, and must include the following elements:

- Data source (e.g., controlled clinical trials, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies, case series)
- Number of subjects

[18] See FDA's reviewer guidance, *Evaluating the Risks of Drug Exposure in Human Pregnancies*.

- Study duration
- Exposure information (timing, duration, and dose of exposure)
- Limitations of the data, including potential confounders and biases, if known

Individual case reports are rarely sufficient to characterize risk and therefore ordinarily should not be included in this section.

If available, data from the comparator or control group, and data confidence intervals and power calculations should also be included.

b. Animal data

This portion of labeling describes the nonclinical developmental toxicity studies that form the scientific basis for any risk statement(s) in the Risk Summary that are based on animal data. The labeling must describe the following (§ 201.57(c)(9)(i)(D)(4)):

- Types of studies
- Animal species
- Animal doses or exposures described in terms of human dose or exposure equivalents and the basis for those calculations
- Duration and timing of exposure
- Study findings
- Presence or absence of maternal toxicity
- Limitations of the data

Descriptions of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes (§ 201.57(c)(9)(i)(D)(4)). However, for vaccines, developmental toxicity studies do not include dose-response evaluations and, therefore, the descriptions of maternal and offspring outcomes will be different for such products.

In evaluating and interpreting nonclinical data, various factors may affect the level of concern raised by a positive signal. These factors include:

- Cross-species concordance of developmental effects
- Multiplicity of effects[19]
- Adverse effects on different stages of the development process
- The relationship between maternal and developmental toxicity
- The presence of a dose-response relationship
- Observation of rare events
- Similarity between pharmacologic and developmental toxicologic mechanisms
- Concordance of the animal and human metabolic and general toxicity profiles
- Relative animal to human exposure

[19] Multiplicity of effects refers to the number of different adverse developmental outcomes. See FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns*.

- Positive signals in other drugs in class or with the same mechanism of action
- Presence or absence of maternal toxicity

The presence or absence of these factors can increase or decrease concern, and some factors can carry greater weight than others. For specific guidance on how to interpret nonclinical developmental toxicity data, see FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns*.

B. 8.2 Lactation

Information in the **Lactation** subsection of labeling, which replaces the **Nursing mothers** subsection, is presented under the following subheadings:

- Risk Summary
- Clinical Considerations
- Data

The PLLR uses the term *lactation* to refer to the biological state during which a woman's body produces and excretes milk. The PLLR uses the term *breastfeeding* to refer to all *human milk feeding* situations when an infant or child is fed with human milk whether the milk is received directly from the breast or as expressed milk.[20] For the purposes of the PLLR and this guidance, the term *drug* or *drug product* is used to refer to human prescription drugs and biological products that are regulated as drugs. It is assumed that drug levels in human breast milk will be collected on the drug, prodrug and the active metabolite(s).

1. Risk Summary

The Risk Summary subheading is always required because certain statements are required to be included even when there are no data or information available (§ 201.57(c)(9)(ii)(A)). The Risk Summary subheading should summarize information on the presence of a drug and/or its active metabolite(s) in human milk, the effects of a drug and/or its active metabolite(s) on the breastfed child, and the effects of a drug and/or its active metabolite(s) on milk production (§ 201.57(c)(9)(ii)(A)(2)(i)-(iii). When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the Data portion of the **Lactation** subsection where the details of the data are presented (§ 201.57(c)(9)(ii)(A)). When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans (§ 201.57(c)(9)(ii)(A)).

When use of a drug is contraindicated during breastfeeding (e.g., radioactive iodine-containing imaging and therapeutic products), this information must be stated first in the Risk Summary (§ 201.57(c)(9)(ii)(A)). This should be followed by a brief explanation of the risk.

[20] American Academy of Pediatrics Policy Statement. Breastfeeding and the use of human milk. Pediatrics. 2012; 129(3):e827-41.

If data demonstrate that a drug is not systemically absorbed by the mother, the Risk Summary must contain only the following statement (§ 201.57(c)(9)(ii)(A)(1)):

> "(Name of drug) is not absorbed systemically by the mother following (route of administration), and breastfeeding is not expected to result in exposure of the child to (name of drug)."

For situations in which the drug is not absorbed systemically by the mother following one route of administration, but the drug is absorbed systemically by the mother following another route (or other routes) of administration, the above statement should be included for the route of administration resulting in no systemic exposure to the mother. This would be in addition to any statements that are required in the Risk Summary based on data demonstrating that the drug is absorbed systemically following another route (or other routes) of administration.

The following discussion describes the requirements for the Risk Summary if the drug is absorbed systemically by the mother.

a. Presence of drug in human milk

The Risk Summary must state whether the drug and/or its active metabolite(s) are present in human milk (§ 201.57(c)(9)(ii)(A)(2)(i)), and should include a brief description of the available data. If there are no data to assess the presence or absence of a drug and/or its active metabolite(s) in human milk, the Risk Summary must so state (§ 201.57(c)(9)(ii)(A)(2)(i)).

If studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the Risk Summary must state the detection limits of the study assay (§ 201.57(c)(9)(ii)(A)(2)(i)).

If studies demonstrate the presence of a drug and/or its active metabolite(s) in human milk, the Risk Summary must include the concentrations in human milk and the actual or estimated infant daily dose (§ 201.57(c)(9)(ii)(A)(2)(i)). The actual or estimated infant daily dose must be calculated for an infant fed exclusively with human milk and compared to the labeled infant or pediatric dose (if available) or the labeled maternal dose (§ 201.57(c)(9)(ii)(A)(2)(i)). This comparison is especially important when there are safety concerns and the actual or estimated infant daily dose received through breastfeeding approaches the labeled infant or pediatric dose, or there are concerns with the ability of a neonate or infant to adequately metabolize or eliminate the drug and/or its active metabolite(s) due to immature and developing drug metabolic and elimination pathways.

The labeled actual or estimated daily dose is based on an exclusively breastfed infant's intake as it represents the highest potential, relative exposure to the drug through breastfeeding. The actual amount of the drug to which a breastfeeding child is exposed will vary based on a child's intake of complementary foods (including formula).

If studies demonstrate the presence of a drug and/or its active metabolite(s) in human milk but the drug and/or its active metabolite(s) are not expected to be systemically bioavailable to the

breastfed child (e.g., drug is degraded in the gastrointestinal tract or not absorbed), the Risk Summary must describe the disposition of the drug and/or its active metabolite(s) (§ 201.57(c)(9)(ii)(A)(2)(i)).

Lactation data may come from a clinical lactation study(s) or from other sources (e.g., published literature, lactation databases). FDA recognizes that the number of women in a lactation study is usually small. Given population variability in maternal drug doses and resulting human milk drug concentrations, it is important to convey the range of human milk concentrations and actual or estimated infant daily drug dose that is reflected in the data.[21]

If only animal lactation data are available, the Risk Summary must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species (§ 201.57(c)(9)(ii)(A)(2)(i)), with a cross-reference to the Data portion of **Lactation** (§ 201.57(c)(9)(ii)(A)), where the data are fully described (§ 201.57(c)(9)(ii)(C)). Due to species-specific differences in lactation physiology, animal lactation data typically do not reliably predict levels in human milk; however, animal lactation data can be helpful in predicting whether a drug and/or its active metabolite(s) will be present in human milk.

b. Effects of drug on the breastfed child

The Risk Summary must include available information on the likelihood and seriousness of known or predicted effects on the breastfed child from exposure to a drug and/or its active metabolite(s) through human milk and/or from contact with maternal (breast/nipple) skin (for topical products) (§ 201.57(c)(9)(ii)(A)(2)(ii)). The Risk Summary must include information on any systemic and/or local (e.g., gastrointestinal tract) adverse reactions (§ 201.57(c)(9)(ii)(A)(2)(ii)). Pediatric age-related differences in absorption, distribution, metabolism, and elimination of the drug should also be included. Although drugs that are applied topically to the nipple area may not result in maternal systemic absorption and excretion into human milk, a breastfed child may orally absorb drug from contact with maternal skin.

If there are no data to assess the effects of the drug and/or its active metabolite(s) on the breastfed child, the Risk Summary must so state (§ 201.57(c)(9)(ii)(A)(2)(ii)).

c. Effects of drug on milk production/excretion

The Risk Summary must describe the effects of a drug and/or its active metabolite(s) on human milk production/excretion, if such data are available (§ 201.57(c)(9)(ii)(A)(2)(iii)). The description can be based on data regarding the pharmacological action of a drug and/or its active metabolite(s) or on clinically relevant data, should specify whether the effect is temporary or permanent.. The Risk Summary must state if no data are available to assess the effects of a drug and/or its active metabolite(s) on milk production/excretion (§ 201.57(c)(9)(ii)(A)(2)(iii)).

[21] FDA has issued a draft guidance on this topic (*Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling)*. Once finalized, it will represent the Agency's thinking on this topic.

d. Risk and benefit statement

For drugs absorbed systemically by the mother, unless breastfeeding is contraindicated during drug therapy, the Risk Summary must include the following risk and benefit statement at the end of the Risk Summary (§ 201.57(c)(9)(ii)(A)(3)):

> "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breastfed child from (name of drug) or from the underlying maternal condition."

The risk and benefit statement provides a basic framework for health care providers and lactating women to use when considering the mother's need for treatment, the benefits of breastfeeding to the mother and to the child, and the potential risks to the child from exposure to a drug and/or its active metabolite(s) through ~~via~~ human milk and/or contact with maternal skin during breastfeeding.

2. Clinical Considerations

The Clinical Considerations subheading must contain the information described below to the extent that the information is available and relevant (§ 201.57(c)(9)(ii)(B)). If there are no data to inform this subheading it should be omitted.

a. Minimizing exposure

Lactation labeling must describe ways to minimize exposure to the breastfed child through human milk and/or contact with maternal skin during breastfeeding if the drug and/or its active metabolite(s): (1) are present in human milk in clinically relevant concentrations, (2) do not have an established safety profile in infants, and (3) are used either intermittently (e.g., acute migraine therapies), in single doses (e.g., radio-imaging drugs, anesthetic agents), or for short courses of therapy (e.g., some antibiotics) (§ 201.57(c)(9)(ii)(B)(1)). When applicable, labeling must also describe interventions to minimize a breastfeeding child's oral intake of topical drugs applied to the breast or nipple skin (§ 201.57(c)(9)(ii)(B)(1)).

Interventions that are intended to minimize exposure of the breastfed child to a drug and/or its active metabolite(s), such as timing the administration of the drug relative to feedings at the breast, pumping sessions, and/or expressing milk in order to discard it ("pump and dump") for a specified time period, should be described when applicable. The specified period should be determined based on available data or on a multiple of the half-life of a drug and/or its active metabolite(s).

A summary of data from clinical lactation studies and/or pharmacokinetic studies can be used to inform this portion of lactation labeling. A cross-reference should be provided to the Data portion of the **Lactation** subsection, where the available clinical lactation study data are described in detail (§ 201.57(c)(9)(ii)(C)). If applicable, a cross-reference can also be provided to CLINICAL PHARMACOLOGY, where available pharmacokinetic data are fully described.

The regulation does not require lactation labeling to describe ways to minimize exposure of the breastfed child to drugs used chronically by lactating women, because it is typically not possible to minimize exposure when the maternal drug and/or its active metabolite(s) are at steady state.

b. Monitoring for adverse reactions

A description of available interventions for monitoring and mitigating drug adverse reactions in the breastfed child that were described in the Risk Summary must be provided in this portion of lactation labeling (§ 201.57(c)(9)(ii)(B)(2)). This information is important for health care providers who are counseling lactating women taking drugs about the relative risks and benefits of breastfeeding to the mother and to the child and about how to monitor for clinically significant drug adverse reactions in the breastfed child.

3. Data

The Data subheading must describe the data on which the Risk Summary and Clinical Considerations are based (§ 201.57(c)(9)(ii)(C)). Applicants must update labeling as new data become available (§ 201.56(a)(2)). Applicants should evaluate the quality and quantity of data available with respect to what information warrants inclusion in labeling.[22] If there are no data, this subheading should be omitted.

C. 8.3 Females and Males of Reproductive Potential

The final rule[23] establishes subsection **8.3 Females and Males of Reproductive Potential** to require information for these populations when (1) there are recommendations or requirements for pregnancy testing and/or contraception before, during, or after drug therapy, and/or (2) there are human and/or animal data suggesting drug-associated effects on fertility and/or pre-implantation loss effects (§ 201.57(c)(9)(iii)). The recommendations and/or requirements for pregnancy testing and/or contraception may be based on concerns for potential or demonstrated adverse developmental outcomes associated with drug exposure during pregnancy. As applicable, the information required under this subsection must appear under the following subheadings, in the following order:

- Pregnancy Testing
- Contraception
- Infertility

If data suggest no adverse effects on fertility, this information should be presented under Infertility.

[22] See FDA's draft guidance, *Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling*.

[23] Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling.

If data from animal studies raise concerns about mutagenesis or impairment of human fertility in females or males, a summary of this information and its clinical implications must appear under **Females and Males of Reproductive Potential**. A cross-reference to NONCLINICAL TOXICOLOGY, for a detailed discussion of the animal studies, should be included.

A subheading should be omitted if not applicable. Subsection 8.3 should be omitted if none of the subheadings are applicable.

V. PROCEDURAL INFORMATION

A. Applications Covered by the Final Rule

The new content and formatting requirements of the final rule apply to any applications (NDA, BLA, or efficacy supplement) that are required to comply with the PLR. As stated in § 201.56(b)(1), this includes:

- prescription drug products for which an application was approved between June 30, 2001, and June 30, 2006,
- prescription drug products for which an application was pending on June 30, 2006, or
- prescription drug products for which an application was or is submitted anytime on or after June 30, 2006.

Holders of applications approved prior to June 30, 2001 (i.e., applications not subject to PLR) are required to remove the pregnancy category from their labeling within 3 years after the effective date of the PLLR.

Although FDA recognizes the effort involved in revising labeling, FDA strongly believes that the PLLR is an important advance in communicating drug information. Therefore, we encourage holders of applications to which the PLLR does not apply to voluntarily convert the labeling of their products to comply with the new content and formatting requirements.

B. Submitting Draft Labeling to FDA for Review

Holders of applications subject to the new content and formatting requirements in the final rule are required to submit the new labeling content in the new format as a prior approval labeling supplement.[24] The required timelines for submitting labeling in the new format are based on the implementation plan (see Appendix B), but applicants are encouraged to voluntarily convert product labeling to the new format prior to the date specified in the implementation plan. Applicants voluntarily revising older labeling would also submit draft labeling as a prior approval labeling supplement. To facilitate FDA's review of labeling, we recommend that the following versions of labeling be submitted as appropriate:

[24] See §§ 314.70(b) and 601.12(f)(1) about supplements requiring FDA approval before the change is made.

- Labeling in the old format
- A clean version (i.e., no redline/strikeout) that complies with the PLLR content and format requirements
- A marked-up version that complies with the PLLR content and format requirements (in redline/strikeout or as tracked changes)
- Microsoft Word versions of all the above

Applicants should explain significant or notable changes in wording or content, or relocation of information to a different section, and how the decisions to make those changes were made. To facilitate identification of the type of submission for the Agency, the applicant should mark clearly on the cover letter, "**Pregnancy and Lactation Labeling/PLLR Conversion**."

If the labeling for applications approved before June 30, 2001 (i.e., applications not subject to PLR) contains a pregnancy category, the application holders are required to remove the pregnancy category by 3 years after the effective date of the final rule and to report the labeling change in their annual reports.[25]

C. Waivers

Applicants may request that FDA waive a labeling requirement under §§ 314.90(a) or 201.58. Applicants should clearly identify the submission as a request for a waiver.

VI. ADDITIONAL LABELING GUIDANCES

FDA has issued several additional guidances for industry on prescription drug labeling. Agency guidance can be found at the web site listed below. This web site is updated regularly as new or revised guidances are published.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm.

[25] See §§ 314.70(d) and 601.12(f)(3) about changes requiring submission in an annual report.

APPENDIX A: ORGANIZATION AND FORMAT FOR PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL SUBSECTIONS

8.1 Pregnancy

Pregnancy Exposure Registry (omit if not applicable)

Risk Summary (required subheading)

Clinical Considerations (omit if none of the headings are applicable)

Disease-associated maternal and/or embryo/fetal risk (omit if not applicable)

Dose adjustments during pregnancy and the postpartum period (omit if not applicable)

Maternal adverse reactions (omit if not applicable)

Fetal/Neonatal adverse reactions (omit if not applicable)

Labor or delivery (omit if not applicable)

Data (omit if none of the headings are applicable)

Human Data (omit if not applicable)

Animal Data (omit if not applicable)

8.2 Lactation

Risk Summary (required subheading)

Clinical Considerations (omit if not applicable)

Data (omit if not applicable)

8.3 Females and Males of Reproductive Potential (omit if none of the subheadings are applicable)

Pregnancy Testing (omit if not applicable)

Contraception (omit if not applicable)

Infertility (omit if not applicable)

APPENDIX B: IMPLEMENTATION PLAN

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 final rule	Time of submission
Applications pending on the effective date of the final rule	4 years after the effective date of the 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 the final rule
Applications approved any time from June 30, 2007, up to and including the effective date of the final rule	4 years after the effective date of the final rule
Applications approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of the final rule

*"Applications" includes NDAs, BLAs, and efficacy supplements.