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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https:///www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Division of Pediatric and Maternal Health (CDER) at 301-796-2200 or the Office of Communication, Outreach, and Development (CBER) at 240-402-8010.

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

July 2020
Labeling
Revision 1

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

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

July 2020
Labeling
Revision 1

TABLE OF CONTENTS

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in complying with the content and format requirements for the *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* subsections of labeling for human prescription drug and biological products.[2] This guidance provides information and recommendations 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.[3]

On December 4, 2014, we published 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).[4] This guidance provides recommendations on complying with the PLLR to applicants with new drug applications (NDAs), biologics license applications (BLAs) (for biological products that are regulated as drugs), and efficacy supplements to approved NDAs or BLAs, as described in greater detail in the final rule and this guidance. This guidance also provides recommendations to applicants that have previously submitted NDAs, BLAs, and efficacy supplements to approved NDAs or BLAs during the time periods specified in the implementation plan in 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, in cooperation with the Center for Biologics Evaluation and Research, at the Food and Drug Administration.

[2] This guidance applies to drugs, including biological drug products, subject to the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006) commonly referred to as the physician labeling rule (PLR). For the purposes of this guidance, the term *drug* or *drug product* will be used to refer to human prescription drugs and biological products that are regulated as drugs.

[3] 21 CFR 201.56(d)(1) and 201.57(c)(9)(i)–(iii).

[4] 21 CFR 201.57(c)(9). See also the final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (79 FR 72064, December 4, 2014).

This guidance revises the draft guidance for industry of the same name issued in December 2014. Changes to this revised draft guidance from that draft guidance include the addition of the following:

- Information on formatting, omitting information, and pregnancy registries, pertinent to PLLR labeling
- Clarifying information related to the Risk Summary heading, risk statements, and human and animal data, pertinent to PLLR labeling
- Information on labeling for subsection 8.3 *Females and Males of Reproductive Potential*, including information on pregnancy testing, contraception, and infertility
- Procedural information on PLLR implementation and submission of draft labeling that complies with PLLR to the Agency for review

In general, FDA's guidance documents 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, in a manner that is clear and useful to providers when prescribing for and counseling patients. Prescribing decisions during pregnancy and lactation are highly individualized and involve complex maternal, fetal, and infant risk-benefit considerations.

The final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (physician labeling rule (PLR)) published January 24, 2006, and revised the requirements for content and format of labeling for human prescription drug and biological products.[5]

The PLLR revises the PLR requirements for subsections 8.1 and 8.2 of prescription drug labeling to provide a framework for clearly communicating information on the risks and benefits of using a drug during pregnancy and lactation to facilitate prescribing decisions. The PLLR also updates the PLR requirements to include a new *Females and Males of Reproductive Potential* subsection to address issues in these populations. The PLLR went into effect on June 30, 2015.

[5] 21 CFR 201.56(d) and 201.57.

The PLLR revised the PLR content and format requirements for subsections 8.1 through 8.3 of the USE IN SPECIFIC POPULATIONS section of labeling as follows:[6,7]

8.1 Pregnancy

This subsection contains information on what is known about the drug's effect on pregnancy, including labor and/or delivery, and replaces the former *Pregnancy* and *Labor and Delivery* subsections.

The PLLR also removed the previously required pregnancy letter 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 could result in inadequately informed clinical decision making. Instead of pregnancy letter categories, under the PLLR, 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 health care providers.

8.2 Lactation

This subsection contains the information that replaces the former subsection, *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 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 described in the NONCLINICAL TOXICOLOGY section, 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 PLLR, *Females and Males of Reproductive Potential,* provides a dedicated subsection that discusses when pregnancy testing or contraception is required or recommended before, during, or after drug therapy, or when there are human and/or animal data that suggest drug-associated fertility effects.

[6] 21 CFR 201.57(c)(9)(i)–(iii).

[7] 21 CFR 201.80 applies to drug products that are not required to convert their labeling to the PLR format. Under the PLLR, drug products subject to 21 CFR 201.80 are only required to remove the pregnancy letter category from their labeling (e.g., "Pregnancy Category C"), but the standard statements that follow each of the pregnancy letter categories (21 CFR 201.80(f)(6)(i)(a-e)) must remain. Accordingly, the PLLR also revised 21 CFR 201.80 by removing the references to the pregnancy letter categories in 21 CFR 201.80(f)(6)(i)(a)–(e).

III. GENERAL PRINCIPLES

A. Revising Labeling

Labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.[8] Consistent with this requirement, applicants should evaluate labeling content when revising existing labeling to comply with the PLLR to ensure that it accurately reflects current knowledge based on systematic review of available evidence. In addition, applicants will typically need to include new content to comply with the PLLR, for example, adding the background rates of birth defects and miscarriage (see section IV. A., 8.1 Pregnancy). Applicants should also review and update other sections of labeling pertinent to the PLLR (e.g., WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY, PATIENT COUNSELING INFORMATION) as necessary when updating the labeling for the PLLR. Subsequent to the initial implementation of the pregnancy and lactation labeling changes required under the PLLR, including the requirements for the *Females and Males of Reproductive Potential* subsection, applicants must continue to keep labeling up to date.[9]

B. Formatting

Subsection numbers and titles in the labeling must be bolded (e.g., **8.1 Pregnancy**).[10] In addition, unique to the PLLR is the requirement for the inclusion of specific headings (e.g., Risk Summary) and when applicable, specific subheadings under headings (e.g., *Labor or Delivery* under Clinical Considerations). The formatting approach used to distinguish headings from subheadings within subsections (e.g., underlining for headings and italics for subheadings) should be consistently used throughout the labeling. Occasionally, information may not fit in the existing headings or subheadings, and the addition of a heading and/or subheading other than those presented in Appendix A can be used to convey important information. If a new heading or subheading is proposed, the applicant should provide justification for the proposed heading or subheading for Agency review.

C. Cross-Referencing

Cross-referencing follows the general principles of the PLR.[11] 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.,

---

[8] 21 CFR 201.56(a)(2).

[9] Ibid.

[10] 21 CFR 201.57(d)(1) and 21 CFR 201.57(d)(7).

[11] For information about the recommended presentation of cross-references in the labeling, see the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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 include pregnancy as a contraindication with a brief description of the observed or anticipated consequences of using the drug during pregnancy and will cross-reference the *Pregnancy* subsection for additional details.[12]

Because the PLLR requires the inclusion of specific headings 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 heading being referenced in parentheses and italics (e.g., (*see Data*)).

D. Omitted Information

In some circumstances applicants must omit certain subsections or specific information otherwise required under the PLLR because it is clearly inapplicable or misleading.[13] For example, if a drug is indicated for use only in neonates, an applicant must omit subsections *Pregnancy* and *Lactation* because this information is clearly inapplicable. The applicant should provide to the Agency the rationale and justification for any proposed PLLR labeling omissions of subsections, headings, subheadings, or specific information required under the PLLR.

IV. SPECIFIC SUBSECTIONS

A. 8.1 Pregnancy

Information in the *Pregnancy* subsection of labeling is presented under the following headings, in the following order:

- Pregnancy Exposure Registry
- Risk Summary
- Clinical Considerations
- Data

[12] For information on how to determine when information related to a PLLR subsection warrants inclusion in the major safety sections of labeling, see the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011).

[13] Under 21 CFR 201.56(a)(2), "labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular." Under 21 CFR 201.56(d)(4), "any section, subsection, or specific information that is clearly inapplicable must be omitted from labeling." For additional information on omitting information in labeling, see the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements.*

1. Pregnancy Exposure Registry

The purpose of including information about a pregnancy exposure registry in the *Pregnancy* subsection is to inform health care providers of the availability of scientifically acceptable pregnancy registries that are consistent with FDA guidance.[14, 15] FDA believes that including information about pregnancy exposure registries in prescription drug labeling will encourage discussions about and participation in registries, thereby improving their usefulness.

If there is a scientifically acceptable pregnancy exposure registry for the drug, the following statement must appear under the heading Pregnancy Exposure Registry:[16]

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

Contact information (e.g., a toll-free telephone number, website) for how to enroll in the registry or obtain information on the registry must also be included under this heading after the required statement.[17] The information under this heading should also reference scientifically acceptable multidrug pregnancy exposure registries, if applicable. A multidrug pregnancy exposure registry actively collects information on exposure to various drug therapies in specific diseases, such as human immunodeficiency virus, epilepsy, or asthma.

Applicants may also consider including the contact information for other pregnancy safety studies that are enrolling patients.

The labeling should also note in the PATIENT COUNSELING INFORMATION section the availability of a pregnancy exposure registry and include a cross-reference to the *Pregnancy* subsection for the contact information for how to enroll.[18]

When a registry is closed or there are changes to the contact information of an existing registry, the labeling must be updated.[19] When there is no active, scientifically acceptable pregnancy exposure registry, the Pregnancy Exposure Registry heading should be omitted.

---

[14] Only registries that are actively enrolling patients should be included in the labeling.

[15] See the draft guidance for industry *Postapproval Pregnancy Safety Studies* (May 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[16] 21 CFR 201.57(c)(9)(i)(A).

[17] Ibid.

[18] See the guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014).

[19] Labeling must be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading (21 CFR § 201.56(a)(2)); see also 21 CFR §§ 314.70 and 601.12.

2. Risk Summary

The Risk Summary heading is required under the *Pregnancy* subsection because certain statements must be included even when no data are available.[20] The labeling under the Risk Summary heading provides risk statement(s) that describe, for the drug, the risk of adverse developmental outcomes based on all relevant human data, animal data, and/or the drug's pharmacology.[21] Because some drugs are metabolized to toxic forms, data on any form of the drug (e.g., drug, prodrug active metabolite) can be applicable in terms of developmental toxicity risk.[22]

Adverse developmental outcomes include the following four groups of developmental toxicities:[23]

- **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

The labeling under the Risk Summary heading is an integrated summary, taking into account relevant information to inform decision-making, and not an individualized listing of available information. When multiple data sources are available, risk statements must be presented in the following order: human, animal, and pharmacologic.[24] In some cases, multiple risk statements may be needed to address the risks 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.

[20] 21 CFR 201.57(c)(9)(i)(B).

[21] Ibid.

[22] See the guidance for industry *Safety Testing of Drug Metabolites* (November 2016).

[23] See the guidance for industry *Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns* (September 2011).

[24] 21 CFR 201.57(c)(9)(i)(B).

When applicable, risk statements must include a cross-reference to additional details in the relevant labeling under the Data heading within the *Pregnancy* subsection.[25]

When use of a drug is contraindicated during pregnancy, this information must be stated first under the Risk Summary heading.[26] A brief description of the observed or anticipated consequences of the contraindicated use should also be included.

If a drug is systemically absorbed, the labeling under the Risk Summary heading must include information about the background risk of major birth defects and miscarriage in the U.S. general population, regardless of drug exposure.[27] Because there is no single comprehensive birth defect surveillance program in the United States, various population-based data sources have been used to estimate the overall prevalence of major birth defects, including the Metropolitan Atlanta Congenital Defects Program[28] and the Texas Birth Defects Registry.[29] These programs vary in methods of ascertainment and goals and objectives. Additional factors that may affect the birth defect rate include maternal age, race/ethnicity, and gestational age. The Centers for Disease Control and Prevention (CDC) reports a major birth defect rate of approximately 3 percent[30] based on pooled data from state-based programs across the United States. These data serve to estimate national rates, indicate regional variations, and describe the epidemiology of specific birth defects. Because various factors may affect the overall major birth defect rate, FDA believes a range of 2 to 4 percent is a reasonable representation of the background major birth defect rate. Miscarriage rates are also affected by factors such as age and have been reported to occur in 15 to 20 percent of clinically recognized pregnancies.[31] If information on birth defects and miscarriage is available for the approved patient population(s) for the drug, that information also must be included.[32] These numbers can change over time. Applicants should periodically review the birth defects and miscarriage data to ensure that the information in the labeling is accurate.[33]

---

[25] Ibid.

[26] Ibid.

[27] 21 CFR 201.57(c)(9)(i)(B).

[28] Rynn L, Cragan J, and Correa A, 2008, Update on Overall Prevalence of Major Birth Defects — Atlanta, Georgia, 1978–2005, MMWR Morb Mortal Wkly Rep, 57(01):1–5.

[29] See the Texas Birth Defects Epidemiology and Surveillance web page available at https://www.dshs.texas.gov/birthdefects/.

[30] See the CDC's Birth Defects web page available at https://www.cdc.gov/ncbddd/birthdefects/data.html.

[31] See American College of Obstetricians and Gynecologists, 2018, Practice Bulletin Number 200: Early Pregnancy Loss, 132(5): e197-207.

[32] 21 CFR 201.57(c)(9)(i)(B).

[33] 21 CFR 201.56(a)(2).

If data demonstrate that a drug is not systemically absorbed following a particular route of administration, the labeling under the Risk Summary heading must contain only the following statement:[34]

> "(*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 approved 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 under the Risk Summary heading 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 establish a drug-associated risk is a complex process that requires an assessment of the quality and quantity of available data.[35] Human data can come from any of the following sources:

- 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 must include the following information about the outcome(s):[36]

- Its incidence[37]
- The effect of dose
- The effect of duration of exposure
- The effect of gestational timing of exposure

[34] 21 CFR 201.57(c)(9)(i)(B).

[35] See the reviewer guidance *Evaluating the Risks of Drug Exposure in Human Pregnancies* (April 2005).

[36] 21 CFR 201.57(c)(9)(i)(B)(1).

[37] The FDA recognizes that some researchers use the term *prevalence* to reflect estimate of birth defect risk.

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 exposed to the drug, but who have the disease or condition for which the drug is indicated to be used. 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.[38]

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 under the Risk Summary heading.[39]

For vaccines,[40] the applicant should consider any risk to the fetus caused by the vaccine's active ingredient(s). 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, if the naturally occurring viral infection in a pregnant woman can cause fetal harm, a live attenuated viral vaccine against that infection may be contraindicated for use 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.[41] This statement must include the following:[42]

- 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

[38] Ibid.

[39] Ibid.

[40] In this guidance, the term *vaccine* refers to vaccines for infectious disease indications.

[41] 21 CFR 201.57(c)(9)(i)(B)(2).

[42] Ibid.

The risk statement must state when animal studies do not meet current standards for nonclinical developmental toxicity studies or when there are no animal data.[43,44]

Toxic drug exposure may be manifested as one type of developmental effect (e.g., embryolethality) 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. There are multiple considerations when determining potential human risks from animal data, including whether an adverse developmental outcome occurs in more than one animal species, especially if the outcome is consistent across species or occurs in the absence of maternal toxicity.[45]

c. Risk statement based on pharmacology

When the drug has a well-understood mechanism of action that may result in adverse developmental outcomes, the risk statement must explain the mechanism of action and the potential associated risks.[46] Examples of well-characterized biochemical and physiologic mechanisms 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). If applicable, a cross-reference should be provided to the applicable subsection(s) of the CLINICAL PHARMACOLOGY section, where the pharmacologic data are more fully described.

3. Clinical Considerations

The labeling under the Clinical Considerations heading[47] provides information to further inform health care providers for prescribing and risk-benefit counseling. Relevant information under the

[43] For a description of current standards for nonclinical developmental toxicity studies, see the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), *S5A Detection of Toxicity to Reproduction for Medicinal Products* (September 1994), and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012). See also the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[44] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[45] See the guidance for industry *Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns*. For vaccines, see the guidance for industry *Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications* (February 2006).

[46] 21 CFR 201.57(c)(9)(i)(B)(3).

[47] 21 CFR 201.57(c)(9)(i)(C).

Clinical Considerations heading is presented under the following five subheadings, to the extent information 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

Subheadings should be omitted if there are no data/information to inform them or the available data/information are not relevant. The Clinical Considerations heading should be omitted in its entirety if all of the subheadings are omitted.

a. Disease-Associated Maternal and/or Embryo/Fetal Risk

The labeling under the Disease-Associated Maternal and/or Embryo/Fetal Risk subheading 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.[48] 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.

An example of a disease with serious risks to the pregnant woman and fetus is diabetes mellitus. Poorly controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, and delivery complications caused by fetal macrosomia (e.g., perineal injury and lacerations, need for cesarean section, postpartum hemorrhage). Poorly controlled diabetes mellitus increases the fetal risk for neural tube defects, cardiovascular malformations, oral clefts, stillbirth, macrosomia-related morbidity (e.g., brachial plexus injury, hypoxia), and neonatal hypoglycemia.

b. Dose Adjustments During Pregnancy and the Postpartum Period

Physiological changes associated with pregnancy may result in pharmacokinetic or other changes significant enough to warrant maternal dosage adjustments. If pharmacokinetic data support dosage adjustment(s) during pregnancy and/or the postpartum period, the labeling must provide a summary of this information under the Dose Adjustments During Pregnancy and the Postpartum Period subheading[49] and should include appropriate cross-references to the specific dosage adjustments recommended in the DOSAGE AND ADMINISTRATION section[50] and to the

[48] 21 CFR 201.57(c)(9)(i)(C)(1).

[49] 21 CFR 201.57(c)(9)(i)(C)(2).

[50] See the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010).

pharmacokinetic study data in the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section.[51]

c. Maternal Adverse Reactions

The labeling under the Maternal Adverse Reactions subheading must provide a summary of drug-associated adverse reactions that are unique to pregnancy or occur with increased frequency or severity in pregnant women,[52] and should include appropriate cross-references to other sections of labeling (e.g., WARNINGS AND PRECAUTIONS,[53] ADVERSE REACTIONS[54]) for additional information. If clinical interventions are available to help monitor or mitigate drug-associated maternal adverse reactions, these interventions must be described under this subheading of labeling[55] (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.[56]

d. Fetal/Neonatal Adverse Reactions

The labeling under the Fetal/Neonatal Adverse Reactions subheading describes fetal/neonatal adverse reactions that are not adverse developmental outcomes and that are not described under the Risk Summary heading. If it is known or anticipated that maternal drug therapy increases or may increase the risk of an adverse reaction in the fetus or neonate (e.g., based on the drug's pharmacologic activity or placental transfer data), the labeling must describe the adverse reaction.[57] 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.[58] If known, the effect of dose, timing, and duration of exposure on the risk must be included.[59]

---

[51] See the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016).

[52] 21 CFR 201.57(c)(9)(i)(C)(3).

[53] See the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format.*

[54] See the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

[55] 21 CFR 201.57(c)(9)(i)(C)(3).

[56] Ibid.

[57] 21 CFR 201.57(c)(9)(i)(C)(4).

[58] Ibid.

[59] Ibid.

For example, opioid analgesics administered during labor may cause reversible respiratory depression in the neonate. Under the Fetal/Neonatal Adverse Reactions subheading, the opioid product labeling should describe this reaction and the appropriate intervention(s).

e. Labor or Delivery

If the drug is expected to affect labor or delivery, the labeling under the Labor or Delivery subheading must provide available information about the drug's effects on the mother and the fetus or neonate, and on the duration of labor and delivery.[60] The labeling under this subheading 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.[61]

For drugs approved for use only during labor and delivery, this subheading (and the information required under this subheading) may be omitted.[62]

4. Data

Under the Data heading in the *Pregnancy* subsection, labeling must describe the data that provide the scientific basis for the information presented under the Risk Summary and Clinical Considerations headings. The Data heading is required, as are the subheadings 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.[63]

a. Human Data

The labeling under the Human Data subheading must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects.[64] Both positive and negative study findings must be included.[65] Applicants should evaluate the quality and quantity of data available with respect to inclusion in labeling.[66, 67]

[60] 21 CFR 201.57(c)(9)(i)(C)(5).

[61] Ibid.

[62] Ibid.

[63] 21 CFR 201.57(c)(9)(i)(D)(2).

[64] 21 CFR 201.57(c)(9)(i)(D)(3).

[65] Ibid.

[66] See the reviewer guidance *Evaluating the Risks of Drug Exposure in Human Pregnancies*.

[67] 21 CFR 201.56(a)(2).

To the extent applicable, the labeling under the Human Data subheading must include the following elements:[68]

- Types of studies or reports (e.g., clinical trials, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies, case series)
- Number of subjects
- Study duration
- Exposure information (e.g., timing, duration, and dose of exposure)
- Limitations of the data, including potential confounders and biases

Quantitative data from the comparator or control groups should be provided, as appropriate.

Individual case reports are rarely sufficient to characterize risk and therefore ordinarily should not be included in this subsection.[69]

b. Animal Data

The labeling under the Animal Data subheading describes the nonclinical developmental toxicity studies that form the scientific basis for risk statement(s) under the Risk Summary heading that are based on animal data. This subheading must describe the following:[70]

- Types of studies
- Animal species
- Dose, duration, and timing of exposure
- Study findings
- Presence or absence of maternal toxicity
- Limitations of the data

[68] 21 CFR 201.57(c)(9)(i)(D)(3).

[69] See the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005).

[70] 21 CFR 201.57(c)(9)(i)(D)(4).

Descriptions of maternal and offspring findings must include dose response and severity of adverse developmental outcomes.[71] However, for certain drug products (e.g., vaccines), developmental toxicity studies do not include dose-response evaluations, and therefore, the descriptions of maternal and offspring outcomes will be different for such drug products. In addition, animal doses or exposures must be described in terms of human dose or exposure equivalents and the basis for those calculations must be included.[72]

In evaluating and interpreting nonclinical data, various factors (e.g., presence or absence of maternal toxicity, relative animal-to-human exposure, multiplicity of effects, positive signals in other drugs in class, with the same mechanism of action) may affect the level of concern raised by a positive signal.[73] The presence or absence of these factors can increase or decrease concern, and some factors can carry greater weight than others.

B. 8.2 Lactation

Information in the Lactation subsection of labeling, which replaces the Nursing Mothers subsection, is presented under the following headings:

- 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.

1. Risk Summary

The Risk Summary heading is required because certain statements are required to be included even when there are no data or information available.[74] The labeling under the Risk Summary heading 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.[75] When relevant human and/or animal lactation data are available, the labeling under the Risk Summary heading must include a cross-reference to the Data heading within the *Lactation* subsection where the details of

[71] Ibid.

[72] Ibid.

[73] For specific guidance on interpreting nonclinical developmental toxicity data, see the guidance for industry *Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns*.

[74] 21 CFR 201.57(c)(9)(ii)(A).

[75] 21 CFR 201.57(c)(9)(ii)(A)(2)(i)–(iii).

the data are presented.[76] When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans.[77]

When use of a drug is contraindicated during breastfeeding, this information must be stated first under the Risk Summary heading.[78] This information should be followed by a brief description of the observed or anticipated consequences of the contraindicated use.

If data demonstrate that a drug is not systemically absorbed by the mother, the labeling under the Risk Summary heading must contain only the following statement:[79]

> "(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 under the Risk Summary heading 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 labeling under the Risk Summary heading if the drug is absorbed systemically by the mother.

a. Presence of drug in human milk[80]

The labeling under the Risk Summary heading must state whether the drug and/or its active metabolite(s) are present in human milk.[81] If there are no data to assess the presence or absence of a drug and/or its active metabolite(s) in human milk, the labeling under the Risk Summary heading must state this.[82]

---

[76] 21 CFR 201.57(c)(9)(ii)(A).

[77] Ibid.

[78] Ibid.

[79] 21 CFR 201.57(c)(9)(ii)(A)(1).

[80] The information on the drug and/or its active metabolite(s) in human milk should include the pharmacologically and/or toxicologically important forms of the drug (i.e., drug, prodrug, and metabolite(s) when relevant).

[81] 21 CFR 201.57(c)(9)(ii)(A)(2)(i).

[82] Ibid.

If studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the labeling under the Risk Summary heading must state the detection limits of the study assay(s).[83]

If studies demonstrate the presence of a drug and/or its active metabolite(s) in human milk, the labeling under the Risk Summary heading must include the concentrations in human milk and the actual or estimated infant daily dose.[84] 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.[85] 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 when there are concerns about the ability of a neonate or infant to adequately metabolize or eliminate the drug and/or its active metabolite(s) because of immature and developing drug metabolism and elimination pathways.

The labeled actual or estimated daily dose is based on an exclusively breastfed infant's intake because it represents the highest potential 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 other food (including infant 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 child's gastrointestinal tract or not absorbed), the labeling under the Risk Summary heading must describe the disposition of the drug and/or its active metabolite(s).[86]

Lactation data may come from a clinical lactation study or studies 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 exposure 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.[87]

If only animal lactation data are available, the labeling under the Risk Summary heading must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk

[83] Ibid.

[84] Ibid.

[85] Ibid.

[86] Ibid.

[87] See the draft guidance for industry *Clinical Lactation Studies — Study Design, Data Analysis, and Recommendations for Labeling* (February 2005). When final, this guidance will represent the FDA's current thinking on this topic.

and specify the animal species,[88] with a cross-reference to the Data heading within the *Lactation* subsection.[89] Drug levels from animal lactation data 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.[90]

b. Effects of drug on the breastfed child

The labeling under the Risk Summary heading 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).[91] Although drugs that are applied topically to the breast/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. The labeling under the Risk Summary heading must include information on any systemic and/or local (e.g., gastrointestinal tract) adverse reactions.[92] A summary of relevant pediatric data on absorption, distribution, and elimination (metabolism and excretion) that could affect safety in the breastfed child should also be included when available.

If there are no data to assess the effects of the drug and/or its active metabolite(s) on the breastfed child, the labeling under the Risk Summary heading must so state.[93]

c. Effects of drug on milk production

The labeling under the Risk Summary heading must describe the effects of a drug and/or its active metabolite(s) on human milk production, if such data are available.[94] 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. The description should specify whether the effect is temporary or permanent. If no data are available to assess the effects of a drug and/or its active metabolite(s) on milk production, the labeling under the Risk Summary heading must state this.[95]

---

[88] 21 CFR 201.57(c)(9)(ii)(A)(2)(i).

[89] 21 CFR 201.57(c)(9)(ii)(A) and (C).

[90] Wang J, Johnson T, Sahin L, Tassinari MS, Anderson PO, Baker TE, Bucci-Rechtweg C, Burckart GJ, Chambers CD, Hale TW, Johnson-Lyles D, Nelson RM, Nguyen C, Pica-Branco D, Ren Z, Sachs H, Sauberan J, Zajicek A, Ito S, Yao LP, 2017, Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary, Clin Pharmacol Ther, 101(6):736–744.

[91] 21 CFR 201.57(c)(9)(ii)(A)(2)(ii).

[92] Ibid.

[93] Ibid.

[94] 21 CFR 201.57(c)(9)(ii)(A)(2)(iii).

[95] Ibid.

d. Risk and benefit statement

For drugs absorbed systemically by the mother, unless breastfeeding is contraindicated during drug therapy, the labeling under the Risk Summary heading must include the following risk and benefit statement at the end of the labeling under the Risk Summary heading:[96]

> "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 human milk and/or contact with maternal skin during breastfeeding.

When the drug is not contraindicated for use in women who are breastfeeding, but breastfeeding is not recommended during drug use because of the potential risk to the breastfed child (e.g., cytotoxic drugs), the labeling should include a statement describing the reason(s) to avoid breastfeeding. Additionally, as noted above, in some circumstances applicants must omit certain subsections or specific information otherwise required under the PLLR because it is misleading;[97] if breastfeeding is not recommended (e.g., cytotoxic drugs), the risk and benefit statement must be omitted if including such a statement would be misleading.[98]

2. Clinical Considerations

The labeling under the Clinical Considerations heading must contain the information described below to the extent that the information is available and relevant.[99] If no data exist to inform this heading, the heading should be omitted.

a. Minimizing exposure

Lactation information in labeling must describe ways to minimize exposure of the breastfed child through human milk 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 intermittently (e.g., acute migraine therapies), in single doses (e.g., radiopharmaceutical

[96] 21 CFR 201.57(c)(9)(ii)(A)(3).

[97] Under 21 CFR 201.56(a)(2), "labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular." For additional information on omitting information in labeling, see the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements.*

[98] See 21 CFR 201.56(a)(2). For more on omitted information, see section III., D., Omitted Information.

[99] 21 CFR 201.57(c)(9)(ii)(B).

and imaging drugs, anesthetic drugs), or for short courses of therapy (e.g., some antibiotics).[100] When applicable, labeling must also describe interventions to minimize a breastfeeding child's oral intake of topical drugs applied to the breast or nipple area.[101]

The labeling should describe, when applicable, 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 to discard it (*pump and dump*) for a specified time period. 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 the labeling under the Clinical Considerations heading in the *Lactation* subsection. A cross-reference should be provided to the Data heading within the *Lactation* subsection, where the available clinical lactation study data are described in detail.[102] If applicable, for pharmacokinetic studies, a cross-reference can also be provided to the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section, where available pharmacokinetic data are fully described.

In general, FDA does not recommend describing 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, which were described in the labeling under the Risk Summary heading, must be provided in the labeling under the Clinical Considerations subsection.[103] 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 adverse drug reactions in the breastfed child.

3. Data

Under the Data heading in the *Lactation* subsection, the labeling must describe the human and/or animal data on which the labeling under the Risk Summary and Clinical Considerations headings are based.[104] When the labeling under the Risk Summary heading is based on human data,

[100] 21 CFR 201.57(c)(9)(ii)(B)(1).

[101] Ibid.

[102] 21 CFR 201.57(c)(9)(ii)(C).

[103] 21 CFR 201.57(c)(9)(ii)(B)(2).

[104] 21 CFR 201.57(c)(9)(ii)(C).

animal data must not be included unless the animal model is specifically known to be predictive for humans.[105] Applicants should evaluate the quality and quantity of data available with respect to what information warrants inclusion in labeling[106, 107] If there are no data, the Data heading under the *Lactation* subsection should be omitted.

C. 8.3 Females and Males of Reproductive Potential

The PLLR established the *Females and Males of Reproductive Potential* subsection of labeling and requires 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.[108] 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. Below is a further description of the appropriate format and content for the *Females and Males of Reproductive Potential* subsection. Circumstances in which pregnancy testing and contraception are required fall under risk evaluation and mitigation strategies.

As applicable, the information required under this subsection must appear under the following headings, in the following order:[109]

- Pregnancy Testing
- Contraception
- Infertility

A heading should be omitted if there are no recommendations or requirements for pregnancy testing and/or contraception or no clinically relevant data on a drug's effects on human fertility. The *Females and Males of Reproductive Potential* subsection should be omitted entirely if all of the headings are inapplicable.

---

[105] 21 CFR 201.57(c)(9)(ii)(A).

[106] See the draft guidance for industry *Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling*. When final, this guidance will represent the FDA's current thinking on this topic.

[107] 21 CFR 201.56(a)(2).

[108] 21 CFR 201.57(c)(9)(iii).

[109] 21 CFR 201.57(c)(9)(iii).

1. Pregnancy Testing

When FDA has determined that pregnancy testing is required[110] or recommended before, during, or after drug therapy for the appropriate use of a drug with potential risk of adverse developmental outcomes, the labeling under the Pregnancy Testing heading must include this information.[111] When pregnancy testing is recommended, consider including a statement that clarifies to the health care provider that the timing and frequency of pregnancy testing and the type of pregnancy test used should be individualized to the patient and is dependent on the chosen contraceptive method.

A statement regarding pregnancy testing should also be added to other sections of labeling, as applicable (e.g., DOSAGE AND ADMINISTRATION) if pregnancy testing is required or recommended.[112]

2. Contraception

When FDA has determined that contraception is required or recommended before, during, or after drug therapy for the appropriate use of a drug with potential risk of adverse developmental outcomes, the labeling under the Contraception heading must include this information.[113] This information should also be included in other sections of labeling (e.g., PATIENT COUNSELING INFORMATION).

If data from nonclinical studies or information based on the mechanism of action raise concerns about mutagenesis, a summary of this information and its clinical implications must appear under the Contraception heading.[114] A cross-reference to the *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection of the NONCLINICAL TOXICOLOGY section, when pertinent for a detailed discussion of the nonclinical studies, should be included. If data from the nonclinical studies do not raise concern with respect to mutagenesis, then that information should be described only in the *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection.

If there are pharmacokinetic studies of semen that inform contraception recommendations, a summary statement of pertinent findings and recommendations should be included under the

---

[110] Section 505-1 of the Federal Food, Drug, and Cosmetic Act establishes FDA's risk evaluation and mitigation strategy (REMS) authority. A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks. If FDA determines that a REMS is necessary, the Agency may require one or more REMS elements, which could include elements to assure safe use (ETASU). ETASU may include, among other things, a requirement that the drug be dispensed to patients with evidence or other documentation of safe use conditions, such as a negative pregnancy test.

[111] Ibid.

[112] See the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.*

[113] 21 CFR 201.57(c)(9)(iii).

[114] 21 CFR 201.57(c)(9)(iii).

Contraception heading, followed by a cross-reference to the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section for a more detailed study description.

In addition, there may be instances in which drug use information pertinent to females or males of reproductive potential that is not necessarily related to adverse developmental outcomes or infertility may be considered for inclusion in this subsection. For example, if there is a demonstrated interaction between the drug and hormonal contraception, additional information about contraception should be considered for inclusion. Information for consideration could include, for example, a summary statement concerning the interaction and any pertinent clinical recommendation to use a nonhormonal or additional method of contraception. In such cases, the information should appear under the Contraception heading, followed by a cross-reference to the DRUG INTERACTIONS section for a more detailed description of the interaction and, if applicable, to other relevant sections of labeling.

3. Infertility

The availability of human data that demonstrate adverse effects of drug exposure on male or female fertility must be described under the Infertility heading.[115] Determining whether available human data can establish a drug-associated risk is a complex process that requires an assessment of the quality and quantity of the data. The Infertility heading also should include a description of what is known about the potential reversibility of the adverse effect(s). Human studies conducted to address potential fertility concerns that do not demonstrate detrimental implications for human fertility should be summarized under the Infertility heading and cross-referenced to the section of the labeling where the detailed study description is provided.

If data from animal studies or information based on the mechanism of action raise concerns about impairment of human fertility, including mutagenesis, and/or pre-implantation loss effects in females or males, a summary of this information and its clinical implications must appear under the Infertility heading.[116] A cross-reference to the *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection of the NONCLINICAL TOXICOLOGY section, when pertinent for a detailed discussion of the animal studies, should be included. If data from the animal studies do not raise concern with respect to impairment of human fertility and/or pre-implantation loss effects, then that information should be described only in the *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection.

[115] 21 CFR 201.57(c)(9)(iii).

[116] Ibid.

V. PROCEDURAL INFORMATION

A. Applications Covered by the Final Rule and Implementation

The content and format requirements of the PLLR apply to applications that are required to comply with the PLR.[117] All NDAs, BLAs, and efficacy supplements approved on or after June 30, 2001, are required to have labeling approved in PLR format.[118] Failure to submit labeling in PLR/PLLR format with an application may be a consideration when deciding whether to refuse to file an application.

The required timelines for submitting proposed labeling in the PLLR content and format are included in Table 1 in Appendix B. The types of applications that are only required to remove the pregnancy letter category in their labeling, and the deadline for doing so, are addressed in Table 2 in Appendix B: Pregnancy and Lactation Labeling Rule (PLLR) Implementation Plan.

Holders of applications approved before June 30, 2001, and for which no efficacy supplements have been approved on or after June 30, 2001 (i.e., applications not subject to PLR), were required to remove the pregnancy category from their labeling within 3 years after the effective date of the PLLR (i.e., by June 30, 2018) and to report the labeling change in their annual reports.[119] Although the pregnancy letter categories were required to be removed from the labeling, the required pre-PLLR standard statements that follow each of the pregnancy letter categories must remain in the labeling.[120]

Applicants not subject to PLR but that submitted a labeling supplement to voluntarily convert to PLR before June 30, 2015 (PLLR effective date), must have removed the pregnancy letter category by June 30, 2018. FDA encourages these applicants to submit proposed labeling to comply with the content and format of PLLR. Applicants not subject to PLR but that have submitted an application to voluntarily convert to PLR on or after June 30, 2015 (PLLR effective date), are required to comply with all content and format requirements of PLR/ PLLR.

FDA encourages holders of applications whose labeling is not subject to PLR to voluntarily convert their labeling to comply with PLR/PLLR. Although FDA recognizes the effort involved in revising labeling, FDA strongly believes that PLR/PLLR is an important advance in communicating drug information.

B. Submitting Draft Labeling to FDA for Review

Holders of applications subject to the PLLR content and formatting requirements and applicants submitting voluntary PLR/PLLR labeling conversions are required to submit the proposed

[117] 21 CFR 201.56(b)(1) and (c).

[118] Ibid.

[119] See 21 CFR 314.70(d)(2) and 601.12(f)(3) about changes requiring submission in an annual report.

[120] 21 CFR 201.80(f)(6)(i).

labeling content as a prior approval supplement.[121] Applicants subject to PLR are required to convert their labeling to the new PLLR content and formatting requirements[122] and should not remove the pregnancy letter categories before submitting revised labeling with the new PLLR content and format. To facilitate FDA's review of labeling, we recommend that the following versions of labeling be submitted (in Microsoft Word file format), as appropriate:

- Last approved labeling
- A clean version containing the proposed changes (i.e., no redline/strikeout)
- A marked-up version that includes proposed changes to the last approved prescribing information (e.g., changes that comply with the PLR/PLLR content and format requirements) as tracked changes
- An annotated version of the prescribing information that includes annotations that support all proposed revisions, including annual reportable changes (Microsoft Word or Adobe PDF file format)

Applicants should explain significant or notable changes in wording or content, relocation of information to a different section or subsection, and how the decisions to make those changes were made.

The submission should include the following:

- A review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication)
- A cumulative review and summary of relevant cases reported in the applicant's pharmacovigilance database (from the time of drug product development to present)
- A summary of drug utilization rates among females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval (if applicable)
- An interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry (if applicable) or other study

If applicants believe the information is not applicable, they should provide justification. Otherwise, this information should be located in Module 1 of the eCTD.

[121] See 21 CFR 314.70(b)(2)(v) and 601.12(f)(1).

[122] 79 FR 72064 at 72095-96.

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**" and locate the labeling and review of current available evidence in Module 1.

C. Waivers and Extensions

Applicants may request that FDA waive a labeling requirement under certain circumstances.[123] The Agency also may consider, on a case-by-case basis, requests for an extension of the required submission date of proposed labeling that complies with PLLR format and content. Applicants should submit a formal waiver or extension request, with a clear rationale, to their marketing applications or supplements and clearly identify the request for a PLLR waiver or extension in the cover letter.

FDA anticipates that waivers, if any, from the PLLR requirements will be granted only in rare circumstances and/or for a limited duration. In addition, FDA anticipates that extensions of the required submission date will be granted only under extenuating circumstances (e.g., completion of a pregnancy registry for which the report will be finalized within 6 months) and for a limited duration. Consistent with this, in general, FDA does not intend to grant such extension requests in situations where a marketing of a drug product has been discontinued and an applicant is seeking an extension until such time as the applicant begins remarketing the drug product.

[123] See 21 CFR 201.58 (providing for waivers of labeling requirements with respect to content and format of labeling for human prescription drug and biological products described in 21 CFR 201.56(b)(1)); see also 21 CFR 314.90(a) (providing for waivers of the NDA requirements under 21 CFR 314.50 through 314.81).

APPENDIX A: ORGANIZATION AND FORMAT FOR PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL SUBSECTIONS[1]

The following information outlines the headings and subheadings (as applicable) for subsections 8.1 through 8.3 of the USE IN SPECIFIC POPULATIONS section of labeling as stated in the pregnancy and lactation labeling rule (PLLR).

8.1 Pregnancy

Pregnancy Exposure Registry

Risk Summary

Clinical Considerations

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

Data

Human Data

Animal Data

8.2 Lactation

Risk Summary

Clinical Considerations

Data

[1] There may be circumstances in which certain subsections, headings, subheadings, or specific information otherwise required under the final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," (pregnancy and lactation labeling rule or PLLR) is omitted because this information is clearly inapplicable or misleading, or informative data are not available. For more on omitted information, refer to section III., D., of this guidance.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Contraception

Infertility

APPENDIX B: PREGNANCY AND LACTATION LABELING RULE (PLLR) IMPLEMENTATION PLAN

The tables below describe the pregnancy and lactation labeling rule (PLLR)[1] implementation plan and timelines for the types of applications required to conform to PLLR content and format requirements (see Table 1) and the types of applications only required to remove the pregnancy letter category (see Table 2).

Table 1: Applications[a] Required To Conform to PLLR Content and Format[b]

Types of Applications[a]	Applications[a] Required To Conform to PLLR Content and Format	Time by Which Labeling With PLLR Content and Format Must Be Submitted to FDA for Approval
New applications	Initially submitted on or after 6/30/2015	At time of submission of new application*
Applications approved 6/30/2001 through 6/30/2015 or pending on 6/30/2015	Approved 6/30/2001 through 6/29/2002 Approved 6/30/2005 through 6/29/2007	6/30/2018
	Approved 6/30/2007 through 6/30/2015	6/30/2019[c]
	Pending on 6/30/2015	
	Approved 6/30/2002 through 6/29/2005	6/30/2020
NDAs or BLAs approved before 6/30/2001 (with no ES approved on or after 6/30/2001)	Voluntary PLR[d] conversion originally submitted on or after 6/30/2015	At time of submission of voluntary PLR conversion labeling supplement

[a] The term *applications* includes 505(b)(1) and 505(b)(2) new drug applications (NDAs), 351(a) and 351(k) biologics license applications (BLAs), and efficacy supplements (ESes).
[b] See the final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," (PLLR) published December 4, 2014, for all the PLLR content and format requirements.
[c] For NDAs, BLAs, or ESs *pending* on 6/30/2015, the required submission date for PLLR format and content is 6/30/2019 or at the time of approval (whichever is later).
[d] The final rule "Requirements on Content and Format of Labeling for Human Prescription Drug Biological Products" (physician labeling rule (PLR)) published January 24, 2006 (21 CFR 201.56, 201.57, and 201.80) describes the scope of applications subject to the requirements (see 21 CFR 201.56(d)). The Agency encourages applicants with applications not otherwise subject to the PLR requirements to voluntarily convert their labeling to the PLR content and format.

[1] The final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," (commonly known as PLLR) published December 4, 2014. The PLLR requirements are found in 21 CFR 201.57(c)(9).

Table 2: Applications Required to Only Remove the Pregnancy Letter Category

Types of NDAs and BLAs[a]	PLR[b] Conversions	Recommendations	Requirement
NDAs or BLAs approved before 6/30/2001 (with no ES approved on or after 6/30/2001)	Voluntary PLR conversion originally submitted before 6/30/2015[c]	Not required (but encouraged) to convert to **PLLR format**	Must have removed pregnancy category by 6/29/2018[d]
	Labeling is in non-PLR format[e] and no voluntary PLR conversion was ever submitted	Not required (but encouraged) to convert to **PLR** and **PLLR format**	

[a] NDA = new drug application; BLA = biologics license application; ES = efficacy supplement.
[b] The final rule "Requirements on Content and Format of Labeling for Human Prescription Drug Biological Products" (physician labeling rule (PLR)) published January 24, 2006 (21 CFR 201.56, 201.57, and 201.80) describes the scope of applications subject to the requirements (see 21 CFR 201.56(d)). The Agency encourages applicants with applications not otherwise subject to the PLR requirements to voluntarily convert their labeling to the PLR content and format.
[c] Effective date for the PLLR.
[d] Although the pregnancy letter categories must be removed from the labeling, the standard statements required by 21 CFR 201.80(f)(6) that follow each of the pregnancy letter categories must remain in the labeling. Applicants must include removal of the pregnancy letter categories in the annual report. See 21 CFR 314.70(d)(2) and 601.12(f)(3) about changes requiring submission in an annual report.
[e] See 21 CFR 201.56(e) and 201.80.