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

*(Small Entity Compliance Guide)*

**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)**

**June 2015  
Labeling**

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

## ***(Small Entity Compliance Guide)***

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

## **Guidance for Industry<sup>1</sup>**

*(Small Entity Compliance Guide)*

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create 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 help small businesses better understand and comply with the 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.<sup>2</sup> 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, or final rule, 79 FR 72064).<sup>3</sup> The final rule requires that the former “Pregnancy,” “Labor and delivery,” and “Nursing mothers” subsections of the USE IN SPECIFIC POPULATIONS section of the

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<sup>1</sup> 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.

<sup>2</sup> This guidance applies to drugs, including biological drug products. For the purposes of the PLLR and this guidance, *drug* or *drug product* will be 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) are applicable in terms of developmental toxicity risk.

<sup>3</sup> In addition to reviewing the final rule, we recommend that small businesses review the draft guidance for industry we issued concurrently with the publication of the PLLR to help drug and biological product manufacturers comply with the new labeling content and format requirements: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products*. 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 Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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labeling for human prescription drug and biological products be replaced by the three subsections entitled *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential*.

FDA has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121).

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**

The requirements on content and format of labeling for human prescription drug and biological products were revised by the January 24, 2006, final rule,<sup>4</sup> commonly referred to as the Physician Labeling Rule (PLR).<sup>5</sup>

In the *Federal Register* of May 29, 2008 (73 FR 30831), we issued a proposed rule to amend the PLR content and format requirements of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the USE IN SPECIFIC POPULATIONS section of labeling for human prescription drug and biological products, which appear in § 201.57 (21 CFR 201.57).

In the *Federal Register* of December 4, 2014 (79 FR 72064), we published a final rule (PLLR) that amended our regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the USE IN SPECIFIC POPULATIONS section of labeling for human prescription drug and biological products.

- The PLLR requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling.
- The PLLR also revises the PLR content and format requirements for subsections 8.1 through 8.3 (now *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential*) of section 8 USE IN SPECIFIC POPULATIONS of the full prescribing information (FPI) (21 CFR 201.57(c)(9)(i) through (c)(9)(iii)).

The final rule is effective on June 30, 2015. The citations to the Code of Federal Regulations (CFR) in this guidance refer to the CFR as amended by the PLLR.

## **III. DESCRIPTION OF PLLR LABELING REQUIREMENTS**

Appendix A of this guidance provides an outline of the organization and format for the *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* subsections of the

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<sup>4</sup> 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).

<sup>5</sup> PLR labeling requirements are described in 21 CFR 201.56 and 201.57.

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PLLR labeling. Below, we describe in more detail the content requirements for these labeling 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
- Data

#### *1. Pregnancy Exposure Registry*

If there is a scientifically acceptable pregnancy exposure registry for the drug,<sup>6</sup> 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 to *8.1 Pregnancy* should be included 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)).

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. If there is more than one risk based on human data, the information should be placed in the order of clinical importance.

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<sup>6</sup> The Agency considers a pregnancy exposure registry scientifically acceptable when it is consistent with FDA guidance. See FDA’s guidance for industry, *Establishing Pregnancy Exposure Registries*.

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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. If information on birth defects and miscarriage is available for the patient population for whom the drug is labeled, the information 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)).

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

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

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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)).

### 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)).<sup>7</sup> 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<sup>8</sup> for nonclinical developmental toxicity studies, or when there are no animal data (§ 201.57(c)(9)(i)(B)(2)).

### 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. A cross-reference should be provided to CLINICAL PHARMACOLOGY, where the pharmacologic data on which this Risk Summary is based are more fully described.

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<sup>7</sup> 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*.

<sup>8</sup> 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*.

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### 3. *Clinical Considerations*

Relevant information under the Clinical Considerations subheading (§ 201.57(c)(9)(i)(C)) is presented under the following five headings, 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

A heading should be omitted if there is no information on the heading topic 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.

#### 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.

#### 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 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

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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)).

### 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, 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.<sup>9</sup> This portion of labeling must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects, and, to the extent available, 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
- Study duration
- Exposure information (timing, duration, and dose of exposure)
- Limitations of the data, including potential confounders and biases, if known

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<sup>9</sup> See FDA's reviewer guidance, *Evaluating the Risks of Drug Exposure in Human Pregnancies*.

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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)).

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

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directly from the breast or as expressed milk.<sup>10</sup> It is assumed that drug levels in human breast milk will be collected on the drug, prodrug, and active metabolite(s).

### *I. 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 information should be followed by a brief explanation of the risk.

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 statement 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

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<sup>10</sup> American Academy of Pediatrics Policy Statement. Breastfeeding and the use of human milk. *Pediatrics*. 2012; 129(3):e827-41.

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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)).

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)).

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 the *Lactation* subsection (§ 201.57(c)(9)(ii)(A)), where the data are fully described (§ 201.57(c)(9)(ii)(C)).

#### **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)).

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 and 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)).

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### 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.

### 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.

#### 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

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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.<sup>11</sup> If there are no data, this subheading should be omitted.

### **C. **8.3 Females and Males of Reproductive Potential****

The final rule 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.

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.

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<sup>11</sup> See FDA's draft guidance, *Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling*.

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### IV. QUESTIONS AND ANSWERS

#### **Question 1: How has the formatting for subsections 8.1 through 8.3 changed under the PLLR?**

The PLLR merges the former *8.1 Pregnancy* subsection and *8.2 Labor and delivery* subsection into a single *8.1 Pregnancy* subsection, which will now include information about labor and delivery.

Under the PLLR, the former subsection *8.3 Nursing mothers* is replaced by subsection *8.2 Lactation*.

Under the PLLR, there also is a new subsection *8.3 Females and Males of Reproductive Potential*, which provides information on pregnancy testing, contraception, and infertility.

Subsection numbers and titles in the FPI must be bolded (e.g., **8.1 Pregnancy**) (§ 201.57(d)(7)). In addition, as outlined in Appendix A to this guidance, there is a requirement under the PLLR for the inclusion of specific subheadings and headings under subheadings within subsections (e.g., Risk Summary). Additional subdivisions of information other than those presented in Appendix A are not recommended.

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*)).

#### **Question 2: How has the content for these subsections changed?**

The final rule requires the removal of the pregnancy categories — A, B, C, D, and X — from all human prescription drug and biological product labeling.<sup>12</sup>

The final rule replaces the pregnancy letter categories with three subsections that provide details about use of the drug in the *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* (if applicable) subsections.

The *Pregnancy* subsection requires information about a pregnancy exposure registry, if one exists. It also must include a summary of the risks of using a drug during pregnancy and relevant

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<sup>12</sup> Section 201.80 (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 § 201.80 by removing the references to the pregnancy letter categories in § 201.80(f)(6)(i)(a)-(e).

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information, if it is available, to help health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy.

The *Lactation* subsection must provide information about using the drug while breastfeeding, such as the amount of the drug in breast milk and potential effects on the breastfed infant.

The *Females and Males of Reproductive Potential* subsection is a new subsection in labeling and must include, when applicable, information about the need for pregnancy testing, contraception recommendations, and information about drug-associated fertility effects.

In addition, the *Pregnancy* and *Lactation* subsections will include three subheadings: “Risk Summary,” “Clinical Considerations” and “Data.” The subheadings are intended to describe, for example, human, animal, and pharmacologic data on use of the drug in these populations, specific adverse reactions in these populations, and information about dose adjustments during the pregnancy and postpartum periods.

### **Question 3: Who must comply with the final rule?**

All holders of applications (NDA, BLA, or efficacy supplement), including those approved prior to June 30, 2001 (i.e., applications not subject to PLR), are required to remove the pregnancy categories from their labeling.

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

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

### **Question 4: When must holders of applications comply with the PLLR requirements?**

The final rule is effective June 30, 2015. There is a phase-in period for holders of applications to comply with the new labeling requirements. The required timelines for submitting labeling in the new format are based on the implementation schedule in the preamble of the PLLR and is set forth below. NDAs submitted on or after the June 30, 2015, effective date must use the new format upon submission. NDAs, BLAs, or efficacy supplements that are pending with the Agency on the June 30, 2015, effective date must comply within 4 years of the effective date, or at the time of approval, whichever is later. Previously approved NDAs, BLAs, or efficacy supplements that were approved on or after June 30, 2001, have a phased-in implementation schedule from 3 to 5 years.

Holders of applications approved before June 30, 2001, are required to remove the pregnancy category from their labeling within 3 years after the June 30, 2015, effective date.

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**Implementation Plan**

<b>Applications Required To Conform to New Pregnancy/Lactation Content Requirements</b>	<b>Time by Which Labeling With New Pregnancy/Lactation Content Must Be Submitted to FDA for Approval</b>
<u>New or Pending Applications:</u> *	
• 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 June 30, 2015, effective date or at time of approval, whichever is later
<u>Approved Applications Subject to the Physician Labeling Rule:</u>	
• 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” are NDAs, BLAs, and efficacy supplements.

**Question 5: How should draft labeling be submitted 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. To facilitate FDA’s review of labeling, we recommend that the following versions of labeling be submitted as appropriate:

- 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

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pregnancy category by 3 years after the effective date of the final rule and to report the labeling change in their annual reports.<sup>13</sup>

### **Question 6: How does this rule apply to generic drugs?**

The labeling for a product approved under an abbreviated new drug application (ANDA) must be the same as the labeling approved for the reference listed drug (RLD) (with limited exceptions). As a result, if the labeling of an RLD is updated as a result of the final rule, the ANDA labeling must also be revised.

### **Question 7: Can applicants request a waiver of the labeling requirements?**

Applicants may request that FDA waive a labeling requirement under 21 CFR 314.90(a) or 21 CFR 201.58. Applicants should clearly identify the submission as a request for a waiver.

## **V. ADDITIONAL LABELING GUIDANCES**

FDA has issued several additional guidances for industry on prescription drug labeling. These guidances include, but are not limited to, the following:

- *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*
- *Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products*
- *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*
- *Warning and Precautions, Contraindications, and Boxed Warning Sections of Labeling Human Prescription Drug and Biological Products — Content and Format*

Agency guidances 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>

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<sup>13</sup> See §§ 314.70(d) and 601.12(f)(3) about changes requiring submission in an annual report.

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**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)