



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

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RIN 0910-AF11

Content and Format of Labeling for Human Prescription Drug and Biological Products;
Requirements for Pregnancy and Lactation Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. 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. For human prescription drug and biological products subject to the Agency's 2006 Physician Labeling Rule, the final rule requires that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The final rule eliminates the "Labor and delivery" subsection because information about labor and delivery is included in the "Pregnancy" subsection. The final rule requires that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females

and males of reproductive potential. The final rule creates a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential. These revisions will facilitate prescriber counseling for these populations.

DATES: This rule is effective June 30, 2015. See section IV of this document for the implementation dates of this final rule.

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Executive Summary

Purpose of the Regulatory Action

FDA is amending its regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section (under § 201.57 (21 CFR 201.57)) and the "Precautions" section (under § 201.80 (21 CFR 201.80)) of the labeling for human prescription drug and biological products (both referred

to as "drugs" or "drug products" in this final rule). In this rulemaking, the Agency is finalizing many of the provisions in the proposed rule issued on May 29, 2008 (73 FR 30831).

This rulemaking is part of a broad effort by the Agency to improve the content and format of prescription drug labeling. The final rule creates a consistent format for providing information about the risks and benefits of drug use during pregnancy and lactation and by females and males of reproductive potential. FDA's revisions to the content and format requirements for prescription drug and biological product labeling are authorized by the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and by the Public Health Service Act (PHS Act).

Summary of the Major Provisions of the Regulatory Action in Question

The final rule requires that for the labeling of certain drug products (as described in the "Implementation" section of this document), the subsections "Pregnancy," "Nursing mothers," and "Labor and delivery" be replaced by three subsections entitled "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." The final rule also requires the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

"Pregnancy"

The final rule merges the current "Pregnancy" and "Labor and delivery" subsections into a single "Pregnancy" subsection of labeling. If there is a scientifically acceptable pregnancy exposure registry for the drug, the "Pregnancy" subsection must contain a specified statement about the existence of the registry, followed by contact information needed to enroll or to obtain information about the registry. The Agency has concluded that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving data collection in pregnant women. Under "Pregnancy," the final rule also requires that the labeling include a summary of the risks of using a drug during

pregnancy. If data demonstrate that a drug is not absorbed systemically, the "Risk Summary" must contain only a specified statement regarding this fact. If data demonstrate that the drug is absorbed systemically, the "Risk Summary" must include risk statements based on data from all relevant sources (human, animal, and/or pharmacologic), that describe, for the drug, the risk of adverse developmental outcomes.

The labeling must also contain relevant information, if it is available, to help health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy; this could include information on disease-associated maternal and/or embryo/fetal risk, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery. FDA believes that including such information supports health care providers' understanding of drug product risks and benefits and facilitates informed prescribing decisions and patient counseling. The labeling must also describe the data that are the basis for the risk statements and clinical information included in the "Pregnancy" subsection of labeling.

"Lactation"

The final rule requires that the "Lactation" subsection of labeling contain a summary of the risks of using a drug during lactation. If data demonstrate that the drug is not absorbed systemically, this summary must contain only a specified statement regarding this fact. If data demonstrate that the drug is absorbed systemically by the mother, this summary must include, to the extent it is available, relevant information on the presence of the drug in human milk, effects of the drug on the breast-fed child, and effects of the drug on milk production. For drugs absorbed systemically, a risk and benefit statement must appear at the end of the summary of risks, unless breastfeeding is contraindicated during drug therapy. FDA has determined that the

inclusion of a risk and benefit statement will provide a useful framework for health care providers to use when making prescribing decisions for a lactating patient.

The "Lactation" subsection must also include, to the extent information is available, relevant information concerning ways to minimize drug exposure in the breast-fed child in certain situations and concerning available interventions for monitoring or mitigating the adverse reactions presented elsewhere in the labeling. In addition, the labeling must also include pertinent information about the data that are the basis for the risk summary and clinical information included in the "Lactation" subsection of labeling.

"Females and Males of Reproductive Potential"

FDA determined that because there was no consistent placement in the labeling of information about pregnancy testing, contraception, and infertility, it was difficult for health care providers to find this important information that can affect decisionmaking before or during pregnancy. Thus, the final rule requires that the "Females and Males of Reproductive Potential" subsection include relevant information when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest drug-associated fertility effects.

Removal of Pregnancy Categories

Through experience and stakeholder feedback, FDA learned that the pregnancy categories were confusing and did not accurately and consistently communicate differences in degrees of fetal risk. In addition, FDA learned that the pregnancy categories were heavily relied upon by clinicians but were often misinterpreted and misused in that prescribing decisions were being made based on the pregnancy category, rather than an understanding of the underlying information that informed the assignment of the pregnancy category. FDA believes that a

narrative structure for pregnancy labeling, rather than a category system, is best able to capture and convey the potential risks of drug exposure based on animal or human data, or both. FDA has determined that retaining the pregnancy categories is inconsistent with the need to accurately and consistently communicate differences in degrees of fetal risk. Therefore, the final rule requires the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

Costs and Benefits

We estimate that over 10 years with a 7 percent discount rate, the present value of one-time costs of the rule equal \$52.4 million and the present value of the annual costs equal \$14.4 million; with a 3 percent discount rate, the present value of one-time costs equal \$60.1 million and the present value of the annual costs equal \$18.2 million. The present value of the total costs equal \$66.8 million with a 7 percent discount rate and \$78.2 million with a 3 percent discount rate. The annualized costs of the rule total \$9.5 million with a 7 percent discount rate and \$9.2 million with a 3 percent discount rate. The final rule will address issues raised by experts and stakeholders and improve the quality of the affected sections of prescription drug labeling. Better quality prescribing information will enhance the usefulness of the labeling. The public health benefits of the final rule would result from improved health outcomes. However, because we have no information about how improved labeling will affect prescriber behavior and patient outcomes, we are unable to quantify the benefits of the final rule.

Summary of Benefits and Costs of the Final Rule

Total Benefits	Present Value of Total Costs with 3 Percent Discount Rate (\$ mil)	Present Value of Total Costs with 7 Percent Discount Rate (\$ mil)	Total Annualized Costs Over 10 Years with 3 Percent Discount Rate (\$ mil)	Total Annualized Costs Over 10 Years with 7 Percent Discount Rate (\$ mil)
Not estimated	78.2	66.8	9.2	9.5

I. Background

In the Federal Register of May 29, 2008 (73 FR 30831), FDA issued a proposed rule to amend 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, which appear in § 201.57. The proposed rulemaking was part of a broad effort by the Agency to improve the content and formatting of prescription drug labeling.

A. History of FDA-Approved Pregnancy and Lactation Labeling for Prescription Drugs

Under sections 502 and 505 of the FD&C Act (21 U.S.C. 352 and 355), FDA has responsibility for ensuring that prescription drug and biological products (both referred to as "drugs" or "drug products" in this final rule) are accompanied by labeling (including prescribing information) that summarizes scientific information concerning their safe and effective use. FDA regulations on labeling for use during pregnancy, during labor and delivery, and by nursing mothers were originally issued in 1979 as part of a rule prescribing the content and format for labeling for human prescription drugs (part 201 (21 CFR part 201)) (44 FR 37434, June 26, 1979) (the 1979 regulations).¹ The requirements on content and format of labeling for drug products were revised on January 24, 2006, in the final rule on "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922), commonly referred to as the "Physician Labeling Rule" (PLR).² As part of the January 2006 revision, the subsections of the labeling on pregnancy, labor and delivery, and nursing mothers were moved from the "Precautions" section under § 201.57 to the "Use in Specific Populations" section. The content of these sections in part 201 was not revised, but the sections were

¹ Thus, the labeling for drugs originally approved before 1979 may not contain the information required by those regulations regarding pregnancy, labor and delivery, and nursing mothers.

² FDA's regulations governing the content and format of labeling for human prescription drug and biological products are contained in §§ 201.56, 201.57, and 201.80.

redesignated as § 201.57(c)(9)(i) through (c)(9)(iii). The previous labeling regulation (adopted in 1979) was redesignated as § 201.80, and applies to products not affected by the January 2006, revisions. In redesignated § 201.80, the subsections on pregnancy, labor and delivery, and nursing mothers are § 201.80(f)(6) through (f)(8).

The 1979 regulations provided, at what was redesignated in 2006 as § 201.57(c)(9)(i) and § 201.80(f)(6)(i), that unless a drug was not absorbed systemically and was not known to have a potential for indirect harm to a fetus, a "Pregnancy" subsection must be included within the "Precautions" section of the labeling. The 1979 regulations required that the "Pregnancy" subsection contain information on the drug's teratogenic effects and other effects on reproduction and pregnancy and, when available, a description of human studies with the drug and data on its effects on later growth, development, and functional maturation of the child. The 1979 regulations also required that each product be classified under one of five pregnancy categories (A, B, C, D, or X) on the basis of risk of reproductive and developmental adverse effects or, for certain categories, on the basis of such risk weighed against potential benefit.³

With regard to labor and delivery, the 1979 regulations stated, at what was redesignated in 2006 as § 201.57(c)(9)(ii) and § 201.80(f)(7), that under certain circumstances, the labeling must include information on the effects of the drug on, among other things, the mother and the fetus, the duration of labor and delivery, and the effect of the drug on the later growth, development, and functional maturation of the child.

With regard to labeling on lactation, the 1979 regulations required, at what was redesignated in 2006 as § 201.57(c)(9)(iii) and § 201.80(f)(8), that a "Nursing mothers" subsection be included in the "Precautions" section of the labeling. The "Nursing mothers" subsection provided that if a drug was absorbed systemically, the labeling must contain

³ For further discussion of the pregnancy categories, see 73 FR 30831 at 30832 through 30833.

information about excretion of the drug in human milk and effects on the nursing infant, as well as a description of any pertinent adverse effects observed in animal offspring. The "Nursing mothers" subsection required the use of certain standard statements depending on whether the drug was known to be excreted in human milk and whether it was associated with serious adverse reactions.⁴

B. Development of the Proposed Rule

Over a number of years after the 1979 regulations were issued, FDA received feedback on the issues and concerns with the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of prescription drug labeling as defined by the 1979 regulations. In response to this feedback, FDA held a part 15 public hearing, conducted focus groups, and convened two advisory committees to provide expert input. During this process, many stakeholders stated that these subsections of prescription drug labeling lacked clarity, often failed to provide meaningful clinical information about drug exposure during pregnancy and lactation, and did not address the potential maternal and fetal consequences of discontinuing needed maternal drug therapy during pregnancy. Experts and other stakeholders noted that the pregnancy categories, although highly relied upon by health care providers, were often misinterpreted and misused. FDA also sought input on the development of a model format for these subsections of labeling, and the resulting model served as the basis for the May 29, 2008, proposed rule (73 FR 30831). The preamble to the proposed rule contains a detailed discussion about the background of the development of the proposed rule and additional details regarding the 1979 regulations governing labeling of drug products for use during pregnancy, during labor and delivery, and while nursing (73 FR 30831 at 30832-30838).

⁴ For further discussion of the history of both the "Pregnancy" and the "Nursing mothers" subsections of prescription drug labeling, see 73 FR 30831 at 30833.

C. The Proposed Rule

FDA proposed to amend the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of physician labeling for prescription drug products subject to § 201.57. The Agency's proposed changes were intended to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that would be useful for decisionmaking by health care providers and their patients. With respect to the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Precautions" section of prescription drug labeling for drug products subject to § 201.80, the Agency proposed only to remove the pregnancy category from the "Pregnancy" subsection.

1. Proposed Provisions for New and Recently Approved Drugs

FDA proposed the following format and content changes to the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of prescription drug labeling for products subject to § 201.57.

- Merge the current "Pregnancy" and "Labor and delivery" subsections into a single "Pregnancy" subsection designated 8.1 under the section "8 Use in Specific Populations."
- Rename the "Nursing mothers" subsection as "Lactation" designated with the identifying number 8.2 under the section "8 Use in Specific Populations."
- Reserve the identifying number 8.3 for future use.
- Replace the format and content of the "Pregnancy" subsection in its entirety with the following:

- If there is a pregnancy exposure registry for the drug, the telephone number or other information needed to enroll in the registry or to obtain information about the registry must be included at the beginning of the "Pregnancy" subsection of labeling.
- Require the inclusion of a general statement about background risk, specifically "All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes (name of drug)'s potential to increase the risk of developmental abnormalities above the background risk."
- Under the subheading "Fetal Risk Summary," require the labeling to contain a risk conclusion and a narrative description of the risk(s) (if the risk conclusion is based on human data).
- Require the fetal risk summary to characterize the likelihood that the drug increases the risk of developmental abnormalities and other risks in humans.
- Require that if data demonstrate that a drug is not systemically absorbed, the fetal risk summary contain only the following statement: (Name of drug) is not absorbed systemically from (part of body) and cannot be detected in the blood. Maternal use is not expected to result in fetal exposure to the drug.
- When both human and animal data are available, require that risk conclusions based on human data be presented before risk conclusions based on animal data. Require that a risk conclusion based on human data be followed by a narrative description of the risks.
- When human data are sufficient to reasonably determine the likelihood that the drug increases the risk of fetal developmental abnormalities or specific developmental

- abnormalities, require the labeling to contain one of two risk conclusions: Human data do not indicate that (name of drug) increases the risk of (type of developmental abnormality or specific developmental abnormality) or Human data indicate that (name of drug) increases the risk of (type of developmental abnormality or specific developmental abnormality).
- When human data are available but not sufficient to reasonably determine the drug's effects on fetal developmental abnormalities, require the labeling to characterize the likelihood that the drug increases the risk of developmental abnormalities as low, moderate, or high.
 - Require that when the data on which the risk conclusion is based are animal data, the fetal risk summary characterize the likelihood that the drug increases the risk of developmental abnormalities using one of the following risk conclusions: Not predicted to increase the risk, low likelihood of increased risk, moderate likelihood of increased risk, high likelihood of increased risk, or insufficient animal data on which to assess the likelihood of increased risk.
 - When human data are available, require that in addition to the risk conclusion(s), the fetal risk summary be followed by a brief narrative description of the risks of developmental abnormalities as well as on other relevant risks associated with the drug.
 - Require the fetal risk summary to refer to the "Contraindications" and/or "Warnings and Precautions" sections of the labeling if there is any information in those sections on an increased risk to the fetus from exposure to the drug.

- Require under the subheading "Clinical Considerations" the inclusion of information about the known or predicted risks to the fetus from inadvertent exposure to the drug, including human or animal data on dose, timing, and duration of exposure. If there are no data to assess the risk from inadvertent exposure, require the labeling to so state.
- Require under the subheading "Clinical Considerations" the inclusion of information related to prescribing decisions for pregnant women, including the risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat and the potential influence of drug treatment on that risk; information about dosing adjustments during pregnancy; if use of the drug is associated with any maternal adverse reactions that are unique to pregnancy or if known adverse reactions occur with increased frequency or severity in pregnant women, a description of such adverse reactions; if it is known or anticipated that treatment of the pregnant woman will cause a complication in the fetus or the neonate, a description of the complication, the severity and reversibility of the complication, and general types of interventions, if any, that may be needed.
- If the drug has a recognized use during labor or delivery, whether or not that use is stated as an indication in the labeling, or is expected to affect labor or delivery, require the inclusion of available information about the effect of the drug on the mother; the fetus/neonate; the duration of labor and delivery; the possibility of complications, including interventions, if any, that may be needed; and the later growth, development, and functional maturation of the child.

- Require the inclusion of a "Data" subheading that, for human data, describes positive and negative experiences during pregnancy, including developmental abnormalities, and, to the extent applicable, the number of subjects and duration of the study. For animal data, require under the subheading "Data" a description of the relationship of the exposure and mechanism of action in the animal species to the anticipated exposure and mechanism of action in humans.
- Replace the "Nursing mothers" subsection with "Lactation" and replace the content requirements of "Nursing mothers" in its entirety with the following:
 - Require that the labeling of all drugs contain a "Lactation" subsection.
 - Under the subheading "Risk Summary," if the data demonstrate that the drug does not affect the quantity and/or quality of human milk and there is reasonable certainty either that the drug is not detectable in human milk or that the amount of drug consumed through breast milk will not adversely affect the breast-fed child, the labeling must state: The use of (name of drug) is compatible with breastfeeding. After this statement (if applicable), the labeling must summarize the drug's effect on milk production, what is known about the presence of the drug in human milk, and the effects on the breast-fed child.
 - The source(s) of the data (e.g., human, animal, in vitro) that are the basis for the "Risk Summary" must be stated. When there are insufficient data or no data to assess the drug's effect on milk production, the presence of the drug in human milk, and/or the effects on the breast-fed child, the "Risk Summary" must so state.
 - If the drug is not systemically absorbed, require that the subheading "Risk Summary" contain only the following statement: (Name of drug) is not absorbed systemically

from (part of body) and cannot be detected in the mother's blood. Therefore, detectable amounts of (name of drug) will not be present in breast milk.

Breastfeeding is not expected to result in fetal exposure to the drug.

- If the drug is absorbed systemically, require the following under the subheading "Risk Summary":
 - A description of the effects of the drug's impact on milk production, including the effect of the drug on the quality and quantity of milk, including milk composition, and the implications of these changes to the breast-fed child.
 - A description of the presence of the drug in human milk in one of the following ways: (1) The drug is not detectable in human milk, (2) the drug has been detected in human milk, (3) the drug is predicted to be present in human milk, (4) the drug is not predicted to be present in human milk, or (5) the data are insufficient to know or predict whether the drug is present in human milk.
 - Require that if studies demonstrate that the drug is not detectable in human milk, the "Risk Summary" state the limits of the assay used.
 - Require that if the drug has been detected in human milk, the "Risk Summary" give the concentration detected in milk in reference to a stated maternal dose (or, if the drug has been labeled for pediatric use, in reference to the pediatric dose), an estimate of the amount of the drug consumed daily by the infant based on an average daily milk consumption of 150 milliliters per kilogram of infant weight per day, and an estimate of the percentage of the maternal dose excreted in human milk.

- Require the inclusion of information about the likelihood and seriousness of known or predicted effects on the breast-fed child from exposure to the drug in human milk based on the pharmacologic and toxicologic profile of the drug, the amount of drug detected or predicted to be found in human milk, and age-related differences in absorption, distribution, metabolism, and elimination.
- Under the subheading "Clinical Considerations," require the labeling to provide the following information to the extent it is available: Information concerning ways to minimize the exposure of the breast-fed child to the drug, such as timing the dose relative to breastfeeding or pumping and discarding milk for a specified period; information about potential drug effects in the breast-fed child that could be useful to caregivers, including recommendations for monitoring or responding to these effects; information about dosing adjustments during lactation.
- Require that the labeling include, under the subheading "Data," an overview of the data that are the basis for the "Risk Summary" and "Clinical Considerations."

2. Pregnancy Categories and Implementation

FDA proposed to require the new content and format changes for prescription drug labeling for all applications (including new drug applications (NDAs), biologics license applications (BLAs), or efficacy supplements) required to comply with the PLR, i.e., for drug products for which an application was approved on or after June 30, 2001. FDA proposed that holders of applications approved before June 30, 2001 (i.e., applications not subject to the PLR), would not be required to implement the new content and format changes. Instead, if the labeling for such applications contains a pregnancy category, the application holders would be required to remove the pregnancy category designation by 3 years after the effective date of the final rule.

D. Mental Models Research

In a separate but related effort, FDA contracted with a third party research firm to conduct a Mental Models Research study in 2009 to better understand the decisionmaking processes of health care providers prescribing drugs to pregnant and lactating women with chronic conditions (Ref. 1). Mental Models Research is an established risk analysis approach that evaluates, using a structured interview, decisionmaking practices that require the synthesis of complex issues. The specific objectives of this study, which involved interviews with 54 health care providers, were to understand how health care providers used FDA-approved prescribing information (in the labeling format in place at the time of the study in 2009), in order to determine the factors that influence their treatment decisions for pregnant and lactating women with chronic conditions, and to define measures that could be used to quantify the value of prescribing information as a tool for these decision makers.

The findings from the Mental Models Research were consistent with the feedback the Agency received during its work on the proposed and final rules. For example, the research showed that the pregnancy categories were relied upon by many health care providers almost to the exclusion of other information found in the labeling. It also showed that providers often relied on secondary sources to find the pregnancy category for a particular product rather than using the product's labeling. Interviewees made suggestions for improving prescribing information, including simplifying the information presented, centralizing the relevant information, and making the information included in labeling clinically relevant.

II. Overview of the Final Rule, Including Significant Changes to the Proposed Rule

A. Overview

In this rulemaking, the Agency finalizes many of the provisions in the May 2008 proposed rule. In addition, the final rule reflects revisions the Agency made in response to comments on the May 2008 proposed rule. FDA has also made editorial and organizational changes to clarify provisions. For the purposes of this rulemaking, the term "drug" or "drug product" is used to refer to human prescription drugs and biological products that are regulated as drugs.

The final rule requires that for the labeling of certain products (as described in the "Implementation" section of this document), the subsections "Pregnancy," "Nursing mothers," and "Labor and delivery" be replaced by three subsections entitled "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." Information previously placed in "Labor and delivery" is required to be included in the "Pregnancy" subsection of labeling. The final rule requires "Risk Summary" subheadings in the "Pregnancy" and "Lactation" subsections of labeling. The "Pregnancy Exposure Registry" subheading under "Pregnancy" is only required if there is such a registry. The "Clinical Considerations" and "Data" subheadings are required under "Pregnancy" and under "Lactation" only to the extent relevant information is available. If data demonstrate that the drug is systemically absorbed, the "Risk Summary" in the "Pregnancy" subsection requires a statement regarding the background risk, in addition to certain other information, and the "Risk Summary" in the "Lactation" subsection of labeling requires the inclusion of a risk and benefit statement, unless breastfeeding is contraindicated. The "Females and Males of Reproductive Potential" subsection is not required if none of the subheadings are applicable. However, when pregnancy testing and/or contraception is required or recommended

before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects, the "Females and Males of Reproductive Potential" subsection requires the inclusion of such information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility," respectively. The final rule also requires statements acknowledging when data on various labeling elements either are not available or do not establish the presence or absence of drug-associated risk. In addition, the final rule requires removal of pregnancy categories from all drug product labeling, including those products for which an application was approved before June 30, 2001.

B. Significant Changes to the Proposed Rule

The final rule reflects revisions to the proposed rule in response to comments received on the proposed rule, as discussed in detail in section III of this document. FDA made the following organizational and content-based changes to the proposed rule:

1. Pregnancy

- The final rule revises the proposed rule to clarify that the "Risk Summary" subheading is always required in the "Pregnancy" subsection of labeling. The subheading "Pregnancy Exposure Registry" is only required when such a registry exists; the "Clinical Considerations" and "Data" subheadings are required when relevant information is available. If the "Clinical Considerations" subheading is required, the following headings under it are also required to the extent relevant 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," and "Labor or delivery." Similarly, if the "Data" subheading is required, the headings

"Human Data" and "Animal Data" are required under it to the extent relevant information is available.

- The final rule revises the proposed "Pregnancy Exposure Registry" subheading as follows:
 - Requires that contact information and a standard statement on the pregnancy exposure registry will be included under its own subheading "Pregnancy Exposure Registry" if there is a pregnancy registry that is scientifically acceptable.
 - Eliminates the phrase "must be stated at the beginning of the 'Pregnancy' subsection of the labeling."
 - Revises the phrase "telephone number or other information needed to enroll" to "contact information needed to enroll."
 - Adds a requirement that the following statement be included in labeling before the contact information for the pregnancy exposure registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy.
- The final rule revises the proposed "Fetal Risk Summary" as follows:
 - Changes the title of the subheading "Fetal Risk Summary" to "Risk Summary."
 - Eliminates the requirement that the following background risk statement be included in the labeling before the fetal risk summary: All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes (name of drug)'s potential to increase the risk of developmental abnormalities above the background risk.

- Replaces the proposed standardized background risk statement with the requirement that, if the drug is systemically absorbed, the labeling state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. The final rule also requires that if such information is available for the population(s) for which the drug is labeled, it must also be included.
- Replaces the term "developmental abnormalities" with the term "adverse developmental outcomes." The final rule defines "adverse developmental outcomes" as structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, and alterations to growth.
- Clarifies that, when applicable, risk statements must include a cross-reference to additional details located under the "Data" subheading of "Pregnancy."
- Revises the statement required when a drug is not systemically absorbed as follows:
 - Replaces the phrase "from (part of the body)" with "following (route of administration)" to describe how the drug enters the body.
 - Replaces the phrase "cannot be detected in the blood" with "maternal use is not expected to result in fetal exposure to the drug."
- Adds a requirement that when use of the drug is contraindicated during pregnancy, this must be stated first in the "Risk Summary."
- Requires that risk statements be presented in the following order: Based on human data, based on animal data, based on pharmacology.
- The "Risk conclusions based on human data" in the "Risk Summary" is revised as follows:

- Replaces the term "risk conclusions" with "risk statement."
- Eliminates the term "sufficient human data" and the proposed rule's requirement that the labeling contain one of the following standardized risk conclusions about sufficient human data: Human data do not indicate that (name of drug) increases the risk of (type of developmental abnormality or specific abnormality) and Human data indicate that (name of drug) increases the risk of (type of developmental abnormality or specific abnormality).
- Replaces the standardized risk conclusions based on human data with the requirement that when human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the Risk Summary must summarize the specific developmental outcome, its incidence, and the effects of dose, duration of exposure, and gestational timing of exposure. The final rule also requires that if the 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), then the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population.
- Requires that the "Risk Summary" must state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

- Eliminates the term "other human data" and the requirement that when there are other human data, the likelihood that the drug increases the risk of developmental abnormalities must be characterized as low, moderate, or high.
- The "Risk conclusions based on animal data" in the "Risk Summary" is revised as follows:
 - Replaces the term "risk conclusions" with "risk statement."
 - Eliminates the requirement that animal data be characterized as "not predicted to increase the risk," "low likelihood of increased risk," "moderate likelihood of increased risk," or "high likelihood of increased risk."
 - Requires that when animal data are available, the labeling must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. The final rule requires that the risk statement include: The number and type(s) of species affected, the timing of exposure, animal doses expressed in terms of human exposure or dose equivalents, and outcomes for pregnant animals and offspring. When animal studies do not meet current standards for nonclinical developmental toxicity studies, the labeling must so state. The final rule requires that when there are no animal data, the "Risk Summary" must so state.
- Adds a "Risk statement based on pharmacology" to the "Risk Summary," requiring that when the drug has a well-understood mechanism of action that may result in drug-associated adverse developmental outcome(s), the "Risk Summary" must explain the mechanism of action and the potential associated risks.
- Eliminates the "Narrative description of human data" requirement from the "Risk

Summary."

- Removes the requirement that the "Risk Summary" refer to the "Contraindications" or "Warnings and Precautions" sections of the labeling when those sections contain information on an increased risk to the fetus from exposure to the drug.
- The final rule revises the "Clinical Considerations" component as follows:
 - Requires headings, to the extent relevant information is available, for "Disease-associated maternal and/or embryo/fetal risk," "Dose adjustments during pregnancy and the postpartum period," "Maternal adverse reactions," "Fetal/Neonatal adverse reactions," and "Labor or delivery".
 - Eliminates the "Inadvertent exposure during pregnancy" heading.
 - Eliminates the "Prescribing decisions for pregnant women" heading.
 - Revises "risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat" (which was the language used in the proposed rule under the "Prescribing decisions for pregnant women" heading) to "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 to be used" and places this information under the new heading "Disease-associated maternal and/or embryo/fetal risk."
 - Under "Dose adjustments during pregnancy and the postpartum period," requires the inclusion of information about dose adjustments during pregnancy and the postpartum period if supported by pharmacokinetic data.

- Under "Dose adjustments during pregnancy and the postpartum period," removes the requirement that, if there are no data on dosing in pregnancy, the labeling must so state.
- Under "Maternal adverse reactions," replaces the proposed requirement that the "labeling must describe any interventions that may be needed (e.g., monitoring blood glucose for a drug that causes hyperglycemia in pregnancy)" with the requirement that the labeling include a description of available intervention(s) for monitoring or mitigating the reaction.
- Adds a requirement that the labeling include relevant information about fetal/neonatal adverse reactions under the heading "Fetal/Neonatal adverse reactions".
- Under "Fetal/Neonatal adverse reactions," replaces the phrase "will cause a complication in the neonate" with "increases or may increase the risk of an adverse reaction in the fetus or neonate."
- Under "Fetal/Neonatal adverse reactions," replaces "the severity and reversibility of the complication" with "the potential severity and reversibility of the adverse reaction," and replaces "general types of interventions, if any, that may be needed" with "available intervention(s) for monitoring or mitigating the reaction."
- Under "Fetal/Neonatal adverse reactions," adds a requirement that the labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk.
- Revises the heading "Drug effects during labor or delivery" to "Labor or delivery."
- Under "Labor or delivery," revises "[i]f the drug has a recognized use during labor or delivery, whether or not the use is stated as an indication in the labeling, or if the drug

- is expected to affect labor or delivery" to "[i]f the drug is expected to affect labor or delivery."
- Under "Labor or delivery," revises "the possibility of complications, including interventions, if any, that may be needed" to "the increased risk of adverse reactions, including their potential severity and reversibility."
 - Under "Labor or delivery," adds a requirement that the labeling provide information about available intervention(s) that can mitigate effects and/or adverse reactions.
 - Under "Labor or delivery," clarifies that the information described under that heading is not required for drugs approved only for use during labor and delivery.
 - Under "Labor or delivery," eliminates the requirement that the labeling include information about the effect of the drug on the later growth, development, and functional maturation of the child.
 - The final rule revises the "Data" subheading of labeling as follows:
 - Replaces "provide an overview of the data that were the basis for the fetal risk summary" with "describe the data that are the basis for the Risk Summary and Clinical Considerations."
 - Requires the inclusion of the subheading "Data," and the headings "Human Data" and "Animal Data," to the extent available information is relied on in the Risk Summary and Clinical Considerations subheadings.
 - Separates the requirements for human data from the requirements for animal data.
 - For human data, requires that the labeling describe adverse developmental outcomes, adverse reactions, and other adverse effects and, to the extent applicable, the types of studies or reports, number of subjects and duration of each study, exposure

- information, and limitations of the data. Requires that both positive and negative study findings be included.
- For animal data, retains the requirement that the labeling describe the types of studies, animal species, dose, duration and timing of exposure, and adds the requirement that the labeling also describe study findings, presence or absence of maternal toxicity, and limitations of the data. Adds the requirement that the description of maternal and offspring findings must include information on the dose-response and severity of adverse developmental outcomes. Requires that animal doses or exposures be described in terms of human dose or exposure equivalents and that the basis for those calculations must be included.

2. Lactation

- The final rule revises the "Risk Summary" as follows:
 - Requires that when relevant human or animal lactation data are available, the "Risk Summary" must include a cross-reference to "Data" in the "Lactation" subsection.
 - Removes the proposed standardized statement "The use of (name of drug) is compatible with breastfeeding."
 - Requires that when human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans.
 - Requires that when use of a drug is contraindicated during breastfeeding, this information must be stated first in the "Risk Summary."
 - Revises the standardized statement required when the drug is not absorbed systemically from (Name of drug) is not absorbed systemically from (part of body) and cannot be detected in the mother's blood. Therefore, detectable amounts of

- (name of drug) will not be present in breast milk. Breastfeeding is not expected to result in fetal exposure to the drug to (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).
- Revises the order of the types of information required if the drug is systemically absorbed as follows: (1) Presence of drug in human milk, (2) effects of drug on the breast-fed child, and (3) effects of drug on milk production.
 - Replaces proposed standardized statements regarding the presence of the drug in human milk with a requirement that the "Risk Summary" state whether the drug and/or its active metabolites are present in human milk, and when there are no data to assess this, the "Risk Summary" must so state.
 - Under "Presence of drug in human milk," requires that if studies demonstrate the presence of the drug and/or its active metabolites in human milk, the "Risk Summary" must state the concentration of the drug and/or its active metabolites in human milk and the actual or estimated daily dose for an infant fed exclusively with human milk. The estimated amount of drug and/or its active metabolites ingested by the infant must be compared to the labeled infant or pediatric dose, if available, or to the maternal dose.
 - Under "Presence of drug in human milk," retains the requirement that if studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the Risk Summary must state the limits of the assay used.
 - Under "Presence of drug in human milk," adds the requirement that if studies demonstrate the presence of the 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 breast-fed child, then the "Risk Summary" must describe the disposition of the drug and/or its active metabolites.

- Adds a requirement that 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.
- Under "Effects of drug on the breast-fed child," the final rule:
 - Adds a requirement that the "Risk Summary" include available information on the known or predicted effects on the child from exposure to the drug and/or its active metabolite(s) through human milk or from contact with breast or nipple skin from a topical product.
 - Requires the inclusion of information about systemic and/or local adverse reactions.
 - Requires that the "Risk Summary" state if there are no data to assess the effects of the drug and/or its active metabolite(s) on the breast-fed child.
- Under "Effects of drug on milk production," the final rule:
 - Replaces the proposed requirement that the "Risk Summary" describe the effect of the drug on the quality and quantity of milk, including milk composition, and the implications of these changes to the milk on the breast-fed child, with the requirement that the "Risk Summary" must describe the effects of the drug and/or its active metabolite(s) on milk production.

- Adds a requirement that when there are no data to assess the effects of the drug and/or its active metabolite(s) on milk production, the "Risk Summary" must so state.
- The final rule adds the requirement that for drugs absorbed systemically, unless breastfeeding is contraindicated during drug therapy, the following risk and benefit statement must appear at the end of the "Risk Summary": 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 breast-fed child from the drug or from the underlying maternal condition.
- Under "Clinical Considerations," the final rule:
 - Revises the provisions of the proposed rule to require that the labeling include information concerning ways to minimize exposure to the drug and/or its active metabolite(s) in the breast-fed child in situations where the following conditions are present: The drug and/or its active metabolite(s) are present in human milk in clinically relevant concentrations; do not have an established safety profile in infants; and are used either intermittently, in single doses, or for short courses of therapy.
 - Adds a requirement that, when applicable, the labeling must describe ways to minimize a breast-fed child's oral intake of topical drugs applied to the breast or nipple skin.
 - Under "Monitoring for adverse reactions," replaces the proposed requirement that the labeling include information about potential drug effects in the breast-fed child that could be useful to caregivers, including recommendations for monitoring or responding to those effects, with a requirement that the labeling must describe

available intervention(s) for monitoring or mitigating the adverse reaction(s) presented in the "Risk Summary."

- Eliminates the proposed requirement that the labeling include information about dosing adjustments during lactation.
- Under "Data," the final rule replaces the phrase "provide an overview of the data" with the phrase "describe the data."

3. Females and Males of Reproductive Potential

- Adds "8.3 Females and Males of Reproductive Potential" subsection requiring that when pregnancy testing and/or contraception are required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects, this subsection of labeling must contain this information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility," in that order.

III. Comments on the Proposed Rule

The Agency received 72 comments on the proposed rule. Comments were received from prescription drug manufacturers, trade organizations representing prescription drug manufacturers and other interested parties, professional associations and organizations representing health care providers, health care and consumer advocacy organizations, individual physicians, pharmacists, consumers, and others.

Most of the comments supported FDA's goal of improving the format and content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of prescription drug labeling, and several of these comments stated that the proposed rule would address shortcomings of the previous labeling regulations. Other comments noted that the proposed rule would improve the accessibility of relevant information, thereby enabling better informed

medical decisions regarding the risks and benefits of prescription drug use by pregnant and lactating women. Although a number of comments supported all of FDA's proposed revisions, many comments opposed particular aspects of the proposed rule.

To make it easier to identify comments and our responses, the word "Comment" and a comment number appear in parentheses before each comment's description, and the word "Response" in parentheses precedes each response. Similar comments are grouped together under the same number. Specific issues raised by the comments and the Agency's responses follow.

A. Proposed Rule as a Whole

1. Plain Language and Intended Audience

(Comment 1) Several comments suggested that the language used in the pregnancy and lactation subsections of prescription drug labeling should be clear and accessible to a variety of audiences. One comment stated that because the intended audience for prescription pregnancy and lactation labeling is females of reproductive potential and their health care providers, this portion of prescription drug labeling should not include overly technical information. Another comment suggested that to make the information more accessible to the general public, FDA should include a plain language summary of the pregnancy and lactation subsections. Two comments suggested that because females of reproductive potential may read the "Pregnancy" and "Lactation" subsections of labeling, FDA should include a statement that encourages patients to always consult a health care provider before discontinuing medication. Another comment questioned how patients would access the proposed information and asked whether it would be included in patient-specific information that patients receive at the pharmacy. Several other

comments suggested that the final rule should aim to create user-friendly labeling that contains a concise and accurate presentation of information that is of clinical relevance.

(Response) FDA acknowledges that some females of reproductive potential may use prescribing information in the "Pregnancy" and "Lactation" subsections of prescription drug labeling. The intended audience of prescription drug labeling, however, is health care providers, and it is the responsibility of the prescribing health care provider to communicate pertinent information regarding drug risks and benefits and proper use to his or her patient. For this reason, we have determined that it is not appropriate to require a summary of the "Pregnancy" and "Lactation" subsections of labeling as a mechanism for all patients to readily access full prescribing information, or a statement that encourages patients to always consult a health care provider before discontinuing medication. We note that in addition to the professional labeling that is the subject of this rulemaking, some drugs also have FDA-approved patient labeling specifically written for the consumer, such as Medication Guides (see 21 CFR part 208). Whether the information required under the final rule will be included in FDA-approved patient labeling for an individual drug will be decided on a case-by-case basis in accordance with the applicable FDA regulations and guidance.

2. Scope of the Rule

(Comment 2) Several comments suggested that FDA expand the scope of the rule in various ways. Two comments suggested that the rule be expanded to include nonprescription products. Four comments suggested that the proposed content changes also apply to drugs for which an application was approved before June 30, 2001, although a separate comment agreed with the proposal to limit the rule to drugs for which an application was approved on or after June 30, 2001. One comment suggested that the rule be expanded to include vaccine products

(we discuss this suggestion later in our response to Comment 8). Two other comments suggested that the rule provide incentives to industry to perform studies on the use of drugs and biological products during pregnancy and lactation. One comment suggested that depression should not be treated pharmacologically during pregnancy, whereas a separate comment suggested that FDA ban the use of all drugs and vaccines during pregnancy. Another comment suggested that the presentation of the information required under the rule be standardized as much as possible with applicable coding schema for ease of implementation in databases or electronic health record systems.

(Response) FDA has considered these comments and declines to expand the scope of the final rule in any of the suggested ways. This final rule amends our labeling regulations in §§ 201.57 and 201.80, which apply only to prescription drug and biological products. It is therefore not within the scope of this rulemaking to address pregnancy and lactation labeling for nonprescription drug products.

The primary purpose of this final rule, and prescription drug labeling in general, is to facilitate informed prescribing and safe and effective product use. FDA recognizes the importance of use of labeling information in electronic health records and other databases and agrees that, if possible, the presentation of information in labeling should facilitate its accessibility. However, this final rule is not designed to standardize the required information with a coding schema for use in databases or electronic health record systems. It is also beyond the scope of this rule to address incentives for collecting data on the use of drugs and biological products during pregnancy and lactation.

FDA does not make recommendations about whether particular diseases or conditions should or should not be treated pharmacologically, though we specifically decline the suggestion

to ban the use of all drugs during pregnancy. We note that many diseases and conditions are associated with adverse pregnancy outcomes when not appropriately managed during pregnancy, and under-treating or not treating a pregnant woman's medical condition may put the woman's health in danger, and is often associated with greater risk to the developing fetus than the risk of exposure to a maternal drug.

FDA also declines the suggestion that the content changes required by this final rule also apply to drugs for which an application was approved before June 30, 2001. In developing this rule, FDA considered the scientific, economic, and practical implications of alternative approaches, including requiring implementation of the content and format requirements for the "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" subsections of labeling for all drugs, regardless of approval date. FDA concluded that requiring the content and format changes only for drugs for which an application was approved on or after June 30, 2001, (as described in the "Implementation" section of this document) best balanced the public health benefits and the economic and other costs of these labeling changes. In addition, this approach provides conformity with the rest of prescription drug labeling and the scope is consistent with the scope of the PLR. FDA, however, encourages voluntary compliance with these content and format changes for drugs for which an application was approved before June 30, 2001.

3. Combining the "Pregnancy" and "Lactation" Subsections

(Comment 3) One comment suggested that the "Pregnancy" and "Lactation" subsections should be combined for certain drugs. The comment explained that combining these sections would be useful, for example, in helping health care providers counsel women who take selective serotonin reuptake inhibitors (SSRIs) for the treatment of perinatal depression because clinicians have to consider the effects of the medication during both pregnancy and the postpartum period.

(Response) FDA disagrees. The risk and benefit considerations for drug product use are different between pregnant and lactating patients, and we have determined that the information is best presented in separate but adjacent subsections of labeling. FDA believes that if the sections were combined it would be more difficult for a health care provider who has either a pregnant or a lactating patient to locate the information relevant to the prescribing decision. For anticipatory counseling, for which the health care provider is discussing the use of the drug with a pregnant patient who in the future may be lactating, we believe that having "Lactation" denoted in a separate, numbered, indexed, and searchable subsection of labeling will not make it harder for a prescriber to find this information.

4. Updates

In the preamble to the proposed rule, FDA stated that under § 201.56(a) "the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading" (73 FR 30831 at 30841). The Agency also explained that "[w]hen new human data concerning the use of a drug during pregnancy becomes available, if that information is clinically relevant, FDA believes that it is necessary for the safe and effective use of the drug and, therefore, the pregnancy subsection of the labeling must be updated to include that information. Failure to include clinically relevant new information about the use of a drug during pregnancy could cause the drug's labeling to become inaccurate, false, or misleading" (73 FR 30831 at 30841).

(Comment 4) Several comments requested that FDA clarify its expectations for the process and timing of updating the "Pregnancy" and "Lactation" subsections of labeling after new data become available. Two of these comments stated that the data should be updated regularly or continually. Another comment stated that the labeling should be updated annually.

Several other comments requested that FDA define the quantity and quality of data that necessitates that the labeling be updated. One of these comments suggested that FDA state in the final rule that the labeling should be updated if the benefit-risk profile changes because of new information, and that labeling changes should be done according to "current labeling regulations." Another comment questioned whether health care providers will be informed of changes to the "Pregnancy" and "Lactation" subsections of labeling. One comment suggested that sponsors electronically post supplemental information before updated printed labeling is available, and another suggested using surveillance systems to facilitate obtaining updated safety information.

Two comments expressed specific concern that the "Lactation" subsection of drug labeling will not be updated frequently enough to be useful for clinicians. One of these comments stated that it is critical to routinely update labeling as human lactation data becomes available. A separate comment suggested including references in labeling to online resources regarding lactation data to provide prescribers and patients with updated information.

(Response) The requirements for labeling updates described in § 201.56(a) apply to this final rule as follows: The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of the chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading (§ 201.56(a)(2)). With respect to the comment about updating labeling as human lactation data becomes available, although § 201.56(a)(3) states that the labeling must be based whenever possible on data derived from human experience, it also requires that conclusions based on animal data but necessary for safe

and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.

Because studies are not usually conducted in pregnant women prior to approval, most of the data regarding use in pregnancy and lactation will be collected in the postmarketing setting. Accordingly, in order that a drug product does not become misbranded, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading. Applicants are responsible for following the medical literature and also for updating labeling as new published and unpublished data become available. FDA declines the suggestion to include references to online resources regarding drug use during lactation because the information has not been reviewed by FDA.

5. Responsibility for Drafting and Reviewing Labeling

(Comment 5) One comment requested that FDA clarify whether industry or FDA would be responsible for writing and reviewing the new labeling. The comment also questioned whether FDA would provide staff with the training and expertise to make necessary judgments. Another comment expressed concern about the potential for inconsistent implementation of the new rule by FDA's review divisions. This comment suggested that to increase labeling consistency, the Agency should establish a group of FDA specialists that review pregnancy and lactation labeling.

(Response) As with all prescription drug labeling, both the manufacturer and FDA reviewers will play a shared role in determining the new labeling content. The Division of Pediatrics and Maternal Health (DPMH), within the Office of New Drugs at the Center for Drug Evaluation and Research, includes staff with expertise in obstetrics, lactation, pediatrics, clinical pharmacy, and regulatory science. The DPMH is available for consultation by all FDA drug

product review divisions to whom the final rule applies for all issues related to labeling content and for review of data on the use of drugs during pregnancy and lactation. The DPMH, by working across review divisions, helps to ensure consistent application of FDA pregnancy and lactation labeling regulations to different drug products. The DPMH also provides consultation services to and works collaboratively with other Offices and Centers at FDA. FDA intends to provide staff with education and training on the changes in the labeling regulations.

6. Process for Development of the Proposed Rule

(Comment 6) One comment stated that FDA should have included pharmacists in the focus tests used during development of the proposed rule.

(Response) FDA acknowledges the critical role that pharmacists play in communicating drug information both to patients and health care providers. However, during the development of the proposed rule, FDA's priority was to understand the information health care providers need to most effectively make prescribing decisions that consider both the risk and benefit to the mother and her fetus or child. Therefore, the focus testing was limited to health care providers who both care for and prescribe for pregnant and lactating women.

7. Guidance on Formulating Labeling

(Comment 7) FDA received one comment requesting that the Agency provide clear guidance to manufacturers regarding how to formulate the pregnancy and lactation labeling subsections.

(Response) Concurrent with the publication of this final rule, FDA is issuing a draft guidance for industry on "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products--Content and Format" (the draft guidance on

pregnancy and lactation labeling).⁵ The draft guidance is intended to assist applicants in drafting the "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" subsections of labeling for prescription drug products. It provides recommendations for applicants revising labeling of already approved products and for applicants drafting labeling for new products that will be submitted as part of an NDA or BLA.

8. Blood Products and Vaccines

(Comment 8) FDA received two comments regarding the applicability of the proposed rule to certain biological products. One comment requested that the final rule be expanded to include vaccine products. The other comment stated that blood products are not affected by the rule and requested that this be noted when the final rule is published.

(Response) This final rule applies to vaccine products. Vaccine products are prophylactic biological products that are developed and labeled to prevent specific diseases in specific populations. The types of information that must be communicated about a vaccine, in general, parallel the types of information that must be communicated about a drug or therapeutic biologic through labeling to facilitate safe and effective use, although there are some unique considerations for vaccines addressed in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with this final rule.

We disagree that blood products are not affected by the final rule. The final rule applies to any biological products, including blood products, that are subject to the PLR.

9. Numbering of "Pregnancy" and "Lactation" Subsections

(Comment 9) FDA proposed that the identifying numbers and titles for the new labeling content under the section "8 Use in Specific Populations" would be 8.1 for "Pregnancy" and 8.2 for "Lactation." FDA stated in the proposed rule that the identifying number 8.3 would be

⁵ This guidance, when finalized, will represent FDA's current thinking on this topic.

available for future use (73 FR 30831 at 30838). Two comments pointed out that under this proposal, the next subsections after "8.2 Lactation" will be "8.4 Pediatric Use" and "8.5 Geriatric Use." These comments stated that the absence of subsection 8.3 may be confusing and suggested that FDA renumber the subsections. One comment requested that FDA clarify whether the Agency has a specific use in mind for 8.3 and, if it does not, suggested that the Agency renumber the subheadings to "8.3 Pediatric Use" and "8.4 Geriatric Use." The comment explained that if a future need for an additional subsection arose, it could become 8.5.

(Response) As discussed in further detail in section III.B of this document, in this final rule, FDA designates 8.3 as "Females and Males of Reproductive Potential." Accordingly, we are no longer reserving 8.3 for future use.

10. International Harmonization

(Comment 10) Two comments suggested that prescription drug labeling should be consistent at an international level to reduce confusion among health care providers, patients, and regulators interpreting the risks and benefits associated with drug use during pregnancy and lactation.

(Response) FDA declines to adopt this suggestion because it is beyond the scope of this rule to address the international harmonization of prescription drug labeling. Although we acknowledge the importance of working with our international regulatory colleagues to harmonize drug development and drug regulatory science where appropriate and beneficial, we also recognize that there is great variation internationally in health care systems, access to care and drugs, and the regulation and marketing of drugs. The final rule reflects our judgment regarding the most useful pregnancy and lactation prescription drug labeling for prescribers in the United States, which may not be applicable to prescribers in all other countries.

11. Examples in an Appendix

(Comment 11) The proposed rule included an appendix containing examples, based on the proposed rule, of pregnancy and lactation labeling for fictitious drugs.

FDA received several comments suggesting that the examples be revised or expanded. One comment requested that in the final rule, FDA provide additional examples of sample labeling, including examples for which extensive data exists. Another comment suggested that the information included in the sample labeling for the fictitious drug products did not reflect the amount of data that is typically available. The comment explained that the examples would be more useful if they presented situations where there is extensive data. Several other comments pointed out that the terminology in the examples was not consistent with the terminology in the proposed rule.

(Response) FDA has not included sample drug labeling with the final rule. The draft guidance on pregnancy and lactation labeling, which is being published concurrently with this final rule, provides information about how to interpret and apply the rule to labeling development. Labeling development is a detailed and iterative process unique to each prescription drug product, a process that is driven by the product's characteristics and actions, the efficacy and safety data submitted to the Agency, and the conditions and populations for and in which the product is intended to be used. Accordingly, FDA has concluded that the development of fictitious product labeling would not be useful to drug developers or FDA reviewers who will be responsible for developing, revising, and approving product labeling under this new final rule.

12. Cross-Referencing

FDA proposed that when the risk conclusion in the fetal risk summary is based solely on animal data, it must include a cross-reference to the "Data" component of the "Pregnancy"

subsection, and the effects found in animals must be described in the "Data" component (73 FR 30831 at 30842).

(Comment 12) One comment suggested that any cross-references to the "Data" or "Clinical Considerations" components made anywhere in labeling specify whether the cross-reference is to the component in the "Pregnancy" subsection or the component in the "Lactation" subsection. Another comment explained that the rule would benefit from extensive use of cross-referencing within the text of each section to ensure that the bases for the risk conclusions are thoroughly understood, regardless of whether the risk conclusions are based on human or animal data, for both the "Pregnancy" and "Lactation" subsections.

(Response) FDA agrees that any cross-references to components of "8.1 Pregnancy" or "8.2 Lactation" must specify whether the cross-reference is to the component in the "Pregnancy" subsection or the component in the "Lactation" subsection. Accordingly, in the final rule, when applicable, risk statements in the "Pregnancy" subsection must include a cross-reference to additional details in the relevant portion of the "Data" subheading in the "Pregnancy" subsection. Also in the final rule, when relevant human and/or animal lactation data are available, the "Risk Summary" must include a cross-reference to the relevant portion of "Data" in the "Lactation" subsection.

13. Need for Educational Campaign

(Comment 13) FDA received one comment suggesting that the Agency develop educational campaigns for patients and health care providers regarding the changes to pregnancy and lactation drug labeling brought about by this rulemaking.

(Response) FDA is developing educational materials for FDA staff, health care providers, and patients to inform them about the changes in these labeling regulations and how these

changes will have a positive impact on labeling regarding the use of drugs and biologics during pregnancy and lactation. The draft guidance on pregnancy and lactation labeling is being published concurrently with this final rule; however, additional materials may be completed following this date.

14. Inventory

(Comment 14) FDA received one comment requesting that the final rule address how distributors should manage drug products in their inventory that have outdated labeling. The comment suggested that product inventory without the revised labeling should remain in the supply chain until the labeled product's expiration date, regardless of whether the product bears the new labeling.

(Response) For previously approved products, the implementation plan gives sponsors a minimum of 3 years after the effective date of this final rule to submit labeling with the new content and format. As we explained in the preamble to the proposed rule, FDA believes that this 3-year period will allow industry sufficient time to use up any existing labeling stock such that none will remain in the supply chain after the product bears the new labeling (73 FR 30831 at 30846).

15. Highlights

FDA's regulations require that all prescription drug labeling described in § 201.56(b)(1) contain "Highlights of prescribing information" (§ 201.57(a)).

(Comment 15) Two comments requested that FDA clarify which elements of the "Pregnancy" and "Lactation" subsections are likely to be included in the "Highlights of prescribing information." One of the comments expressed hope that adoption of the rule will promote standardization with respect to which elements are elevated to the "Highlights of

prescribing information," thereby facilitating consistent interpretation and implementation of the rule's requirements among FDA reviewers and review divisions.

(Response) The requirements for placement of information in the "Highlights of prescribing information" are specified in § 201.57(a). This final rule does not revise or change the requirements for the "Highlights of prescribing information." Additional discussion of FDA's recommendations on the content of the "Highlights of prescribing information" may be found in FDA's guidance for industry on "Labeling for Human Prescription Drug and Biological Products--Implementing the PLR Content and Format Requirements" (February 2013).⁶

16. Preemption of State Law

In the preamble to the proposed rule, FDA included a discussion in the Federalism section that referred to a more extensive discussion and analysis in the PLR regarding the preemption of product liability lawsuits.

(Comment 16) Comments expressed different views about this discussion. One comment suggested that in the final rule FDA revise the preamble to eliminate any reference to the preemption of product liability lawsuits. Another comment expressed its appreciation of FDA's view that the rule would preempt state laws that conflict with its requirements. This comment also expressed its support for FDA's intention to consult with State and local officials in an effort to avoid conflict between State law and federally protected interests.

(Response) FDA's statement regarding preemption in the proposed rule relied on statements made in the preamble to the PLR (71 FR 3922). In the preamble to the PLR, FDA

⁶ U.S. Food and Drug Administration, "Guidance for Industry, Labeling for Human Prescription Drug and Biological Products--Implementing the PLR Content and Format Requirements," (February 2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf>. Many guidances are referenced throughout this document. The guidance referred to in this footnote, as well as others referenced throughout the remainder of the document, can be found on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

discussed its views on the preemptive effect of both that regulation's codified provisions and the FD&C Act. Subsequent to the publication of the May 2008 proposed rule, the Supreme Court, in Wyeth v. Levine (555 U.S. 555 (2009)), addressed the preamble to the PLR and held that a State tort claim that an NDA-approved drug should have had a stronger warning was not preempted by the FD&C Act or FDA's labeling requirements. Following the Court's decision in Wyeth, FDA concluded that the position on preemption we articulated in the preamble to the PLR cannot be justified under legal principles governing preemption (Preemption Review, 76 FR 61565, October 5, 2011). Based on this analysis, to the extent that the discussion in the proposed rule relied on the discussion about preemption in the preamble to the PLR, we conclude that the statements we made regarding preemption in the preamble to the proposed rule are also not justified.

B. Specific Provisions of the Proposed Rule

1. 8.1 Pregnancy

a. Comments related to the pregnancy subsection as a whole.

i. Order of subsections--FDA proposed that information appear in subsection "8.1 Pregnancy" in the following order: (1) Pregnancy exposure registry (if applicable), (2) general statement about background risk, (3) fetal risk summary, (4) clinical considerations, and (5) data (proposed § 201.57(c)(9)(i)). In the proposed rule, FDA sought comment on how these elements should be ordered to optimize the clinical usefulness of this labeling subsection (73 FR 30831 at 30839). Specifically, FDA asked whether the "Fetal Risk Summary" should precede the pregnancy exposure registry information and the statement about background risk.

(Comment 17) Comments expressed different opinions about the proposed order of information in the "Pregnancy" subsection of labeling. Three comments agreed with the

proposed order. One of these comments explained that the proposed order will maximize a physician's ability to find and understand important pregnancy-related information about a given drug product. Another comment explained that placing the pregnancy exposure registry information first is preferable because if this information were placed after the "Risk Summary," it may be interpreted to imply that the pregnancy exposure registry exists because of the data in the fetal risk summary. One comment supported placing the pregnancy exposure registry information first so that it will appear more visible in labeling.

Many comments disagreed with the proposed order and suggested a variety of alternatives. Six comments suggested that the "Fetal Risk Summary" subheading be placed first because it contains the most important and useful information. One of these comments pointed out that past FDA advisory committees have suggested that summary information should be placed first. Two comments suggested that the "Background Risk Statement" should be first followed by the "Fetal Risk Summary." These comments explained that the most important information should be placed first, as recommended by FDA advisory committees. Three comments suggested that the pregnancy exposure registry information be placed last. Another comment suggested that the information be placed in the following order: Pregnancy exposure registry information, clinical considerations, fetal risk summary, data, and background risk statement.

(Response) FDA has determined that placing the pregnancy exposure registry information first under "8.1 Pregnancy" best balances the objectives of this rulemaking. Although we agree that the "Risk Summary" information is most important to prescribers and we acknowledge that the advisory committee expressed a preference for placing the most important information first, it is also clear that stakeholders desire greater quality and quantity of human

data in pregnancy labeling. FDA believes that the benefits of prominently placing information about pregnancy registry availability at the beginning of "8.1 Pregnancy" outweigh the downsides of a minor decreased prominence of the "Risk Summary" information, which appears immediately after the information under "Pregnancy Exposure Registry." Many health care providers are still learning about pregnancy exposure registries and their purpose. We have concluded that routinely placing this information first in pregnancy labeling may increase pregnancy registry enrollment, the quality of human data that emerge from these studies, and the quality of pregnancy labeling (including the "Risk Summary") that follows. Because we agree that the information under "Risk Summary" is most important to prescribers, we also decline the suggestion to place the "Risk Summary" after "Clinical Considerations." The "Pregnancy" subsection will include, in this order, information under "Pregnancy Exposure Registry," as applicable, "Risk Summary," "Clinical Considerations," as applicable, and "Data," as applicable.

ii. Removal of the pregnancy categories--FDA proposed to remove the pregnancy categories from all prescription drug labeling. As discussed in greater detail in section I of this document, in 1979 FDA adopted a pregnancy category system that was used to convey risk and benefit information related to potential or documented human teratogenic risk and potential maternal/fetal benefits associated with drug treatment during pregnancy. Under the 1979 regulations, each drug product was identified with a pregnancy category: A, B, C, D, or X. Categories were not used to characterize the risks and benefits associated with drug treatment by lactating women. FDA proposed to remove pregnancy categories from all prescription drug labeling because we determined that the categories were confusing and did not accurately and consistently communicate differences in degrees of fetal risk (73 FR 30831 at 30846).

(Comment 18) Comments expressed different opinions about whether the elimination of the pregnancy category system, in full or in part, would improve or diminish the usefulness of the Pregnancy subsection of prescription drug labeling. FDA received 11 comments from medical associations, women's and reproductive health advocacy organizations, toxicologists, individual health care practitioners, pharmacists, and drug manufacturers specifically supporting our proposal to retire the pregnancy category system. Several of these comments explained that the categories were confusing or misleading. One of the comments stated that although the use of pregnancy categories is easier for some practitioners, it results in miscommunication and errors in decisionmaking. Another comment explained that reliance on the categories may result in poorly informed clinical decisionmaking.

FDA received 16 comments from physicians, pharmacists, pharmacy associations, nurses, manufacturers, drug safety consultants, and individual consumers, requesting that FDA either retain the pregnancy category system or replace the pregnancy category system with another standardized schema. Many of these comments suggested that FDA add the additional narrative information as proposed, but also retain the category system. Two of these comments explained that the pregnancy categories are simple and effective, and the new information may confuse patients or prescribers. Another comment stated that without a standardized schema, there will not be a consistent and useful format for decisionmaking. Other comments agreed that the pregnancy categories need to be revised but suggested that FDA develop new standardized statements or categories or revise the bases for the current categories. Two comments urged FDA to maintain an "X"-like category for drugs where the risks outweigh any benefit to a pregnant or nursing patient, and one comment urged FDA to maintain an "X"-like category so

that providers and patients could easily identify those drugs that are contraindicated for the mother, fetus, and/or a breastfeeding infant.

A separate comment supported FDA's proposal to eliminate the pregnancy categories but thought they should be retained until the implementation of the final rule is complete.

(Response) FDA has determined that retaining the pregnancy categories is inconsistent with the need to accurately and consistently communicate differences in degrees of fetal risk. As discussed in the proposed rule, the current pregnancy category system has long been criticized as being confusing and overly simplistic (73 FR 30831 at 30833-30834). Through experience and stakeholder feedback, FDA learned that the pregnancy categories were heavily relied upon by clinicians but misinterpreted, misunderstood, and erroneously used as a grading system where fetal risk increased from A to X. The categories gave the incorrect impression that drugs in the same category carried the same risk or potential for human adverse developmental outcomes. In addition, the categories did not discriminate among risk information obtained from nonclinical animal studies and postmarketing human studies and did not discriminate among drugs associated with adverse outcomes of differing severity or incidence. Stakeholders also pointed out that the pregnancy categories focused on structural abnormalities and thus did not adequately address the full range of potential developmental toxicities.

As described in greater length in the preamble of the proposed rule, FDA carefully explored a multitude of models to determine whether the former pregnancy category system or a different pregnancy category system could accurately and consistently communicate differences in degrees of fetal risk (73 FR 30831 at 30833-30837). FDA found that when it applied these criteria to actual animal and human data findings for drugs with known risk profiles, none of the models produced clinically informative and reliable differentiations of risk (73 FR 30831 at

30838). Prescribing and drug-use decisions during pregnancy require consideration of not only fetal risk information, but also of various clinical and individual factors, including maternal drug effects, the severity of maternal disease, maternal tolerance of the drug, coexisting maternal conditions, the impact of maternal disease on the fetus, and available alternative therapies. FDA concluded that continuing to use a category system to characterize the risks of drug use during pregnancy would not be appropriate because of the complexity of medical decisionmaking regarding drug use during pregnancy (73 FR 30831 at 30838).

FDA continues to believe that a narrative structure for pregnancy labeling is best able to capture and convey the potential risks of drug exposure based on animal or human data, or both. This perspective is consistent with FDA's approach to other aspects of product labeling. For example, numeric or letter or other categorical gradations of risk have never been used for safety labeling because safety and risk are complex constructs in clinical medicine. For similar reasons, FDA does not apply symbol or letter designations of risk to other potential toxicities or adverse effects expected with drug product use.

For the reasons discussed previously, FDA declines the suggestion to maintain pregnancy category X. We note, however, that labeling must clearly identify populations in which use of a drug is contraindicated. The labeling regulations in § 201.57 clearly describe the information that must be included in the "Contraindications" section and all contraindications from the full prescribing information are always listed in the "Highlights of prescribing information" (§ 201.57(c)(5)). Therefore, when use of a drug is contraindicated in pregnancy, this information must be stated in the "Contraindications" section and listed in the "Highlights of prescribing information," as well as, per the previous discussion, stated first under the "Risk Summary" subheading of the "Pregnancy" subsection of labeling.

To the extent that the comment suggests that the pregnancy categories should be retained for applications subject to § 201.80 until the implementation of the new content and format requirements is complete, we decline this suggestion; we believe it is more consistent with the Agency's overall concerns with respect to removing the pregnancy categories to implement that change within a shorter timeframe that nevertheless provides sufficient time for compliance. We would like to clarify that for applications required to implement the new content and format requirements, the pregnancy categories are required to be removed at the time the labeling is revised regardless of whether this will result in the labeling including a pregnancy category for more than 3 years after the effective date of the final rule (as described in the "Implementation" section of this document in response to Comment 92). Requiring that the labeling for some applications be revised twice solely as part of the implementation of this regulation would not be consistent with the Agency's goal to avoid overburdening both the Agency and industry.

b. Comments related to specific provisions of 8.1 Pregnancy.

i. Pregnancy exposure registry--FDA proposed that if there is a pregnancy exposure registry for a product described in § 201.56(b)(1) (i.e., prescription drug products for which an application was approved after June 30, 2001), the telephone number or other information necessary to enroll in the registry or to obtain information about the registry must be stated at the beginning of the "Pregnancy" subsection of prescription drug labeling (proposed § 201.57(c)(9)(i)(A)). For drug products that do not have a pregnancy exposure registry, the proposed rule did not require the "Pregnancy" subsection of prescription drug labeling to contain any statement about pregnancy exposure registries.

(Comment 19) Comments disagreed about the mandatory inclusion of pregnancy exposure registry information. Many comments supported the mandatory inclusion of pregnancy

exposure registry information in the "Pregnancy" subsection of prescription drug labeling. These comments explained, for example, that including pregnancy exposure registry information in labeling may "encourage patient involvement in registries" and "pave the way for improved registry use by clinicians leading to better documentation of drug effects and use during pregnancy."

One comment stated that including a reference to an existing pregnancy registry should not be mandatory.

(Response) FDA believes that appropriately conducted pregnancy registries are an important mechanism for the collection of clinically relevant data concerning the effects of exposure to drugs during pregnancy. The Agency believes that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving their usefulness. Thus, if there is a pregnancy registry that FDA has reviewed and found scientifically acceptable, FDA is requiring that the "Pregnancy" subsection of prescription drug labeling include under its own subheading, "Pregnancy Exposure Registry," a standard statement concerning the existence of the registry, as well as the contact information necessary to enroll in the pregnancy exposure registry or to obtain information about the registry. The Agency generally considers a pregnancy exposure registry scientifically acceptable when it is consistent with applicable FDA guidance, including the guidance for industry on "Establishing Pregnancy Exposure Registries" (August 2002). If there are changes to an existing pregnancy registry or a new pregnancy registry is initiated after drug approval, labeling will need to be updated to include this new information.

(Comment 20) Two comments sought clarification regarding the standards for including contact information for a pregnancy exposure registry. One comment stated that contact

information should only be included if the registry is scientifically acceptable to the sponsor and FDA. Another comment asked whether contact information for non-U.S. registries must be included.

(Response) As stated previously, if there is a scientifically acceptable pregnancy registry for a drug product, FDA is requiring a standard statement concerning the registry as well as contact information needed to enroll in the registry or obtain additional information about it. For registries that include U.S. populations, U.S. contact information should be included in the labeling, regardless of whether the registry is maintained within the United States or elsewhere.

(Comment 21) Four comments suggested that the pregnancy exposure registry information should have its own component header.

(Response) FDA agrees with the suggestion that the pregnancy exposure registry information should have its own component header. In the final rule, contact information for an existing pregnancy exposure registry and a standard statement on the registry will fall under the subheading "Pregnancy Exposure Registry" in the "Pregnancy" subsection of prescription drug labeling. Because of this change, FDA eliminated the phrase "must be stated at the beginning of the 'Pregnancy' subsection of the labeling" from the final rule.

(Comment 22) Two comments stated that it should be easier to enroll patients in pregnancy exposure registries.

(Response) The importance of subject recruitment into pregnancy exposure registries and the need to build awareness of pregnancy exposure registries among health care providers are both factors in FDA's decision to place information about existing pregnancy exposure registries at the beginning of § 201.57, "8.1 Pregnancy." The actual process of enrolling patients, however, is beyond the scope of this rule.

(Comment 23) Comments expressed disagreement about whether the "Pregnancy Exposure Registry" subheading should be omitted from the "Pregnancy" subsection of prescription drug labeling when there is no existing registry for the drug. One comment suggested that the "Pregnancy Exposure Registry" subheading should not be omitted even if there is no existing registry for the drug, and that it should include a statement that there is no specific pregnancy exposure registry for the drug. Another comment requested that FDA consider incorporating a statement that the subheading may be omitted if there is no pregnancy exposure registry.

(Response) FDA concludes that the "Pregnancy Exposure Registry" subheading should be omitted when there is no pregnancy exposure registry. We have determined that requiring the "Pregnancy Exposure Registry" subheading in labeling when there is no pregnancy exposure registry for the drug product, and the inclusion of a statement indicating that no registry exists, would not further the goal of improving the collection of data in pregnant women who are exposed to a drug.

(Comment 24) One comment suggested that the labeling should state the purpose of the pregnancy exposure registry and provide the contact information necessary for enrollment.

(Response) FDA agrees that including a statement in the labeling about the purpose of the pregnancy exposure registry would be useful. In the final rule, FDA requires that if there is a scientifically acceptable pregnancy exposure registry for the drug, the labeling must include a statement that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to the drug during pregnancy, and include contact information needed to enroll in the registry or to obtain information about the registry. Because the purpose of all pregnancy registries is to collect clinically relevant human data that can be used in a product's labeling to

provide health care providers with useful information for treating or counseling patients who are pregnant or anticipating pregnancy, we do not believe it is necessary to include a more specific statement in labeling about their purpose.

(Comment 25) Two comments suggested that pregnancy exposure registry information be included in "Highlights" and in the "Patient Counseling Information" section of labeling. One comment requested that FDA clarify in guidance whether the Agency anticipates requesting more pregnancy registries as a condition of marketing approval.

(Response) FDA believes that including information about pregnancy exposure registries in the "Patient Counseling Information" section of labeling would be useful. If the drug product has a pregnancy exposure registry, the availability of a pregnancy exposure registry should be noted in the "Patient Counseling Information" section of labeling, and a cross-reference should be included to "8.1 Pregnancy" for the contact information necessary to enroll. The preamble to the PLR states that "Highlights" summarizes the information from the "Full Prescribing Information" that is most important for prescribing the drug safely and effectively and organizes it into logical groups to enhance accessibility, retention, and access to the more detailed information (71 FR 3922 at 3931). Information about the availability of and contact information for a pregnancy exposure registry are not considered essential information for prescribing and should not appear in "Highlights" (see FDA's guidance for industry on "Labeling for Human Prescription Drug and Biological Products--Implementing the PLR Content and Format Requirements" (February 2013)). The question of whether FDA anticipates requesting more pregnancy exposure registries as a condition of marketing approval is outside the scope of this rule.

In the final rule, FDA revised the phrase "telephone number or other information needed to enroll" to "contact information needed to enroll." FDA determined that this change would allow for more flexibility in the type of contact information included under this portion of the labeling.

ii. Background risk statement--FDA proposed that a general statement about the background risk of adverse pregnancy outcomes be included in labeling. The proposed rule stated in § 201.57(c)(9)(i)(B) that the following statement was required to be included in the labeling: All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes (name of drug)'s potential to increase the risk of developmental abnormalities above the background risk.

(Comment 26) Two comments expressed support for the inclusion of a background risk statement. One of these comments noted that the statement will be useful to clinicians when explaining the fetal risks associated with drug use during pregnancy.

Several comments suggested modifying the background risk statement. One comment suggested that applicants be given the option to identify in the background risk statement the specific risks described in the fetal risk summary. The comment proposed that the second sentence of the background statement be modified to state: "The fetal risk summary below describes the potential of (name of drug) to contribute to risk of ('adverse outcomes, including developmental abnormalities' or identify specific risks) above background risk."

Several comments requested clarification about whether the background risk statement refers to the general population or the population with the disease. Two other comments suggested that when the background risk of adverse outcomes in the relevant disease population is known to be higher than in the general population, this information should be included in the

background risk statement. One of these comments suggested that relevant literature citations should also be included as appropriate.

One comment asked FDA to clarify how it will determine the background rate of adverse pregnancy outcomes. Another comment suggested that FDA and industry develop a standard definition of background risk that would provide a common explanation for all labeling, both for the general population and for any specific disease states or conditions. This comment explained that different reviewers may look at different criteria for assessing background risk (i.e., what constitutes a developmental abnormality or a congenital malformation), and a standard definition would provide for consistency. A separate comment stated that the background risks of pregnancy can vary by demographics, location, ethnicity, and other variables. The comment suggested that to maintain uniform and standardized descriptions of background risk, FDA should provide industry with a guidance document describing background risk.

One comment recommended against requiring data in the background risk statement. The comment explained that background statistics change over time as new evidence is made available and accepted by the medical community.

Several comments suggested that FDA revise or omit the second sentence of the background risk statement. One of the comments explained that the sentence implies that the drug necessarily has the potential to increase the risk of developmental abnormalities above the background risk.

(Response) In the final rule, FDA has eliminated the proposed standardized background risk statement. In its place, the final rule requires that the labeling state the percentage range of live births in the general population of the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug

exposure. The final rule also requires that if such information is available for the population(s) for which the drug is labeled, it must also be included. The final rule requires that the background risk information appear in labeling under the subheading "Risk Summary," rather than as a standalone statement under its own subheading (as in the proposed rule).

The Agency has determined that rather than including a standardized general statement about background risk, it is beneficial to include the approximate background rates of major birth defects and miscarriage. This will provide some context to the risk statement, and a basis for comparison with risk estimates from studies in pregnant women. Including the approximate background rates allows the prescriber to inform patients of the risk of major birth defects and miscarriage, regardless of drug exposure. Accordingly, the final rule requires that the labeling include the approximate background rates of major birth defects and miscarriage, regardless of drug exposure, in the United States. FDA agrees, however, that it is possible that these numbers may change over time. Therefore, the Agency did not include any specific numbers in the final rule. Instead, the Agency has provided information, including relevant literature citations, about current background rates of major birth defects and miscarriage in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with this final rule. Although the literature citations are included in the draft guidance, the Agency does not believe it is either necessary or appropriate to include them in the labeling.

FDA agrees that the second sentence in the proposed background risk statement, which states that the fetal risk summary describes the drug's potential to increase the risk of developmental abnormalities above the background risk, could have been misinterpreted as meaning that the drug is associated with an increased risk. As discussed previously, the Agency

has removed the standardized background risk statement, including the second sentence, from the final rule.

iii. Fetal risk summary--FDA proposed that under "Pregnancy," prescription drug labeling include a subheading "Fetal Risk Summary" (§ 201.57(c)(9)(i)(C)). FDA proposed that the section include a risk conclusion, contain a narrative description of the risk(s) (if the risk conclusion is based on human data), and refer to any contraindications or warnings and precautions.

(Comment 27) One comment expressed support for the proposed "Fetal Risk Summary," explaining that the proposed labeling requirements increase the utility of the "Pregnancy" subsection by expanding the teratology section to include information about specific developmental abnormalities such as incidence, seriousness, reversibility, potential for correction, and effect of dose, duration, and gestational timing of exposure. Several other comments suggested that the proposed "Fetal Risk Summary" be revised in various ways, discussed in detail as follows.

Sources of data. FDA proposed that all available data, including human, animal, and pharmacologic data, that are relevant to assessing the likelihood that a drug will increase the risk of developmental abnormalities and other relevant risks must be considered (Proposed § 201.57(c)(9)(i)(C)(1)).

(Comment 28) One comment recommended that rather than considering "all available data," the data sources for the "Fetal Risk Summary" be limited to "scientifically rigorous, organized data collection schemes such as clinical or preclinical studies, and registries."

(Response) FDA declines this suggestion. For example, depending on the safety signal, valuable information may come from epidemiological studies that are not prospective pregnancy

exposure registries. On occasion, adverse event reporting or case series reporting may raise enough concern about a potential increased risk for a specific structural malformation or pattern of malformations, or a serious adverse event, that the information should be included in labeling.

(Comment 29) Maternal and neonatal risk. One comment suggested that FDA include information regarding maternal and neonatal risks in the "Pregnancy" subsection of labeling. The comment suggested that FDA add a "maternal risk subsection," preferably before the "Fetal Risk Summary," which would address side effects and adverse reactions associated with the use of a drug, including those unique to pregnancy. The comment explained that placing this information higher on the label and making it a separate subsection would underscore the importance of the health of the mother. The comment also suggested that FDA include neonatal outcomes as well as fetal outcomes in the "Fetal Risk Summary."

(Response) FDA agrees that information on drug-associated maternal risk is important, and in the final rule has created a separate heading, "Maternal adverse reactions," under "Clinical Considerations," which requires relevant information, to the extent it is available, about drug-associated maternal adverse reactions that are unique to or more frequent or severe during pregnancy. FDA disagrees that information on neonatal outcomes as well as fetal outcomes should be included in the "Risk Summary." Rather, if available, this information is included under its own heading, "Fetal/Neonatal adverse reactions," under "Clinical Considerations." FDA believes that consistent placement of this information under a specified heading under "Clinical Considerations" will allow health care providers to easily locate this information. FDA also believes that this approach ensures that maternal, fetal, and neonatal risks will be captured and clearly conveyed in prescription drug labeling.

Terms used to describe adverse fetal outcomes. FDA proposed that the fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities in humans (i.e., structural anomalies, fetal and infant mortality, impaired physiologic function, alterations to growth) and other relevant risks (e.g., transplacental carcinogenesis) (proposed § 201.57(c)(9)(i)(C)(1)).

(Comment 30) Several comments suggested that the term "developmental abnormalities" should be replaced with a broader and more accurate term. One comment suggested FDA replace the term "developmental abnormalities" with the term "adverse outcomes, including developmental abnormalities." This comment explained that the phrase "developmental abnormalities" does not include "other relevant risks (e.g., transplacental carcinogenesis)" that are also required to be described in the "Fetal Risk Summary." Several comments suggested replacing the term "developmental abnormalities" with the term "developmental effects" or "adverse developmental effects." These comments explained that in the field of developmental toxicology, a developmental abnormality would imply, in general, a dysmorphogenic effect (malformation or variation), rather than the wider definition intended by the proposed rule. Several comments noted the importance of using terminology consistently in labeling.

(Response) FDA agrees that the terms used to describe various developmental effects or outcomes should be accurate and understandable, and that standard nomenclature in the field of developmental toxicology should be used to the extent that it exists. FDA also agrees that terminology should be used consistently in labeling. FDA concludes that the term "developmental abnormalities" is widely recognizable as referring to structural defects (malformations or variations), rather than the full range of possible manifestations of

developmental toxicity as FDA had intended. Therefore, in the final rule, FDA has included the following terms that describe various developmental toxicities, as explained in the following list:

- "Adverse developmental outcomes" has replaced "developmental abnormalities" as the general term to encompass all manifestations or types of developmental toxicity.
- "Structural abnormalities" is used to describe dysmorphology, which includes malformations, variations, deformations, and disruptions, rather than the proposed "structural anomalies."
- "Embryo-fetal and/or infant mortality" is used to describe developmental mortality, which includes miscarriage, stillbirth, and infant death (including neonatal death), instead of the proposed "fetal and infant mortality."
- "Functional impairment" is used to describe functional toxicity, which includes such outcomes as deafness, endocrinopathy, neurodevelopmental effects, and impairment of reproduction, rather than "impaired physiologic function."
- "Alterations to growth" is used to describe such outcomes as growth restriction, excessive growth, and delayed and early maturations.

These terms and descriptions are consistent with FDA's guidance for industry on "Reproductive and Developmental Toxicities--Integrating Study Results to Assess Concerns" (September 2011).

Relationship between animal and human data. FDA proposed that when both human and animal data are available, risk conclusions based on human data must be presented before risk conclusions based on animal data (proposed § 201.57(c)(9)(i)(C)(2)).

(Comment 31) A number of comments suggested that FDA reexamine the emphasis that the "Fetal Risk Summary" places on human data as compared to animal data.

Several comments stated that because there will be frequent conflicts between human and animal data, FDA should develop an overall approach to characterize risk based on both human and animal data. One of these comments suggested that FDA consider the European Medicines Agency's (EMA's) (now EMA's) Integration Table for Risk Assessment and Recommendation for Use as an example of how to integrate risk conclusions based on animal and human data.

Two comments stated that the proposed rule gives primary emphasis to human studies, if they exist, while downgrading the emphasis on animal data. One of these comments explained that the quality and statistical power of human data often fall well short of desirable, and suggested that human data be accompanied by clear acknowledgement of any deficiencies. The other comment explained that emphasizing minimal human data over strong animal data can misrepresent the fetal risk of a drug.

Two comments suggested that if human data are "insufficient" (i.e., do not meet the standard for inclusion in proposed § 201.57(c)(9)(i)(C)(2)(i)), a risk statement based on human data should not precede a risk statement based on animal data. One of these comments explained that the most robust and clinically relevant data should always be presented first.

Several comments stated that if risk conclusions are based on sufficient human data, sponsors should not be required to include animal data, even if such data are available. One comment also suggested that if sufficient human data become available after the labeling is approved, animal data should be removed when the human data are added to the labeling. This comment explained that "a risk conclusion based on animal data might not support, or could flatly contradict, a risk conclusion based on sufficient human data."

One comment suggested that FDA ban all animal studies because human studies are more accurate.

(Response) We continue to believe that the "Risk Summary" is appropriately based on both human and animal data. Because of the importance of human data, we also have determined that when human data provide an incomplete assessment, this should be stated in the risk statement based on human data. Specifically, the "Risk Summary" must state when there are no human data or when available human data do not establish the presence or absence of a drug-associated risk. FDA believes that the use of narrative summaries of the data will avoid conflicting characterizations of risk magnitude.

FDA disagrees with the suggestion that animal data be presented first in cases where the human data are insufficient. FDA also disagrees that the most robust and clinically relevant data--whether human data or animal data--should always be presented first. We have determined that to promote consistency and to meet readers' expectations that information will always be found in the same place, a fixed order of presentation must be maintained. Moreover, we have determined that human data should precede animal data because it is the most clinically relevant.

We note that the purpose of this rulemaking is to facilitate informed prescribing and safe and effective drug product use; placing restrictions on or encouraging any type of studies that may be used as the basis for drug labeling is beyond the scope of this rule.

Not systemically absorbed. FDA proposed that if the drug is not systemically absorbed, the fetal risk statement must contain only the following statement: (Name of drug) is not absorbed systemically from (part of body) and cannot be detected in the blood. Maternal use is not expected to result in fetal exposure to the drug (proposed § 201.57(c)(9)(i)(C)(1)).

(Comment 32) One comment suggested that this statement should focus on the route of administration rather than the part of the body.

(Response) FDA agrees that "part of the body" could be misconstrued and we have

determined that the use of "route of administration" to describe how the drug enters the body is more consistent with labeling language that addresses dosing and administration. In the final rule, FDA has replaced "part of the body" with "route of administration." FDA has determined that "cannot be detected in the blood" is redundant and that the statement is clear without this phrase. In the final rule, FDA has eliminated that phrase.

(Comment 33) Standard statement for certain drugs. FDA received one comment suggesting that we develop a standard statement for drugs that are indicated for use only by males or by females who are not of reproductive potential.

(Response) FDA disagrees. We have determined that a standard statement is not needed. We believe it is appropriate that the "Risk Summary" will be included in labeling for all drugs, regardless of their indicated population. This will promote consistency in drug labeling.

Risk conclusions based on human data. In the proposed rule, under the subheading "Fetal Risk Summary," FDA proposed that when human data are sufficient to reasonably determine the likelihood that the drug increases the risk of fetal developmental abnormalities or specific developmental abnormalities, the likelihood of increased risk must be characterized using one of the following risk conclusions: Human data do not indicate that (name of drug) increases the risk of (type of developmental abnormality or specific developmental abnormality) or Human data indicate that (name of drug) increases the risk of (type of developmental abnormality or specific abnormality) (proposed § 201.57(c)(9)(i)(C)(2)(i)). The proposed rule defined the sources of "sufficient human data" as clinical trials, pregnancy exposure registries or other large scale epidemiologic studies, or case series reporting a rare event (proposed § 201.57(c)(9)(i)(C)(2)(i)).

(Comment 34) Many comments requested that FDA more clearly define the criteria for "sufficient human data" and provide further guidance on the quantity and quality of evidence considered to be "sufficient human data" rather than "other human data." One comment requested that FDA clarify the standards that constitute "sufficient human data," including how those standards were developed. Another comment stated that there is no agreement among experts as to how much data are needed to reach a risk conclusion and requested that FDA clarify what is considered sufficient human data to reasonably determine the risk of developmental abnormalities. Several comments questioned whether data from an individual study could ever constitute "sufficient human data." These comments explained that although individual clinical trials, pregnancy exposure registries, large-scale epidemiologic studies, and case series can provide signals for potential adverse pregnancy outcomes, an individual study is not statistically powered to fully assess the incidence and form one of the proposed risk conclusions. A separate comment stated that even if human data has multiple sources, there is often not enough human data to make a risk conclusion. This comment questioned how often the risk statements based on sufficient human data would be used. One comment stated that the proposed rule does not discuss who will determine whether the data are sufficient or how such a determination will be made. The comment suggested that to increase consistent implementation across review divisions, a dedicated group of FDA specialists should review the determination of whether the human data are sufficient or insufficient for all labeling subject to the rule. This comment also requested that FDA provide examples of sufficient and insufficient data and that FDA caution prescribers that such classifications should not be considered as scientific proof that a drug may or may not harm a particular patient.

(Response) FDA agrees that the term "sufficient human data" is ambiguous and has eliminated it from the final rule. FDA has also eliminated from the final rule the distinction between "sufficient human data" and "other human data." In the final rule, FDA requires that when human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the labeling must summarize the specific developmental outcome; its incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. As stated previously, the final rule also requires that the "Risk Summary" state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

FDA has also determined that the term "risk conclusion" is inappropriate because the available data may not always lead to a conclusion regarding the drug's risk to the fetus. Therefore, in the final rule, FDA has replaced the term "risk conclusion" with the term "risk statement."

(Comment 35) Several comments suggested that the Agency revise the proposed risk statements to make them more straightforward and appropriately qualify the nature of the data and the inability to draw definitive conclusions about an absence of risk based on them. Two of these comments suggested that the term "human data" be replaced with the term "available human data." One comment suggested that the risk conclusion "Human data do not indicate that (name of drug) increases the risk of (type of developmental abnormality or specific developmental abnormality)" be replaced with "Available human data indicate no additional risk of (type of developmental abnormality or specific developmental abnormality) with (name of drug)." One comment suggested that the term "indicate" should be replaced with the term "suggest."

(Response) In the final rule, FDA has eliminated the requirement in the proposed rule that standardized risk conclusions be used to characterize the likelihood of increased risk. As discussed previously, in the final rule, FDA requires instead, under "Risk statement based on human data," that when human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the labeling must summarize the specific developmental outcome; its incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. The final rule also requires that if the 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. The final rule requires that if the 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, but risk information is not available for women who were not exposed to the drug but who have the disease or condition for which the drug is indicated to be used, then the risk for the specific outcome must be compared to the rate at which the outcome appears in the general population.

(Comment 36) FDA also received comments about the proposed sources of sufficient human data. One comment stated that sufficient data must be based on large-scale epidemiologic studies or clinical trials, and cannot be based on pregnancy registries or case reports/series requiring further evaluation. This comment explained that most pregnancy registries can only serve to rule out a major teratogen and to generally determine the similarity in array of effects seen in large registries, and they cannot provide a quantitative estimate of population rates of individual defects or abnormalities. Another comment stated that a risk

conclusion cannot always be reached based on the types of human data described in the proposed rule, and questioned whether there is a consistent approach to sufficient human data as it relates to case series reporting of a rare event. This comment explained that spontaneous reports should not be part of the basis for this subsection. One comment questioned how the labeling will summarize seemingly contradictory results of well-powered pregnancy exposure registries or studies from which a definitive clinical conclusion cannot be reached.

(Response) FDA recognizes that because retrospective voluntary adverse event reporting may be biased and incomplete, spontaneous reports cannot rule in or out a causal relationship between drug exposure and clinical outcome. However, multiple spontaneous reports (or case series) of rare events can be useful in suggesting possible associations between adverse events and drug exposure during pregnancy that warrant further investigation. Furthermore, FDA has determined that data from studies with small numbers of pregnancy exposures may provide valuable information about potential safety signals, especially when corroborated by findings from other studies.

(Comment 37) One comment suggested that FDA eliminate the proposed rule's requirement that sponsors specify all possible types of developmental abnormalities or specific abnormalities for which human data do not indicate that the drug increases the risk. The comment explained that such a list could be lengthy and of little clinical benefit to health care providers.

(Response) FDA did not intend to imply that every potential type of developmental abnormality must be included in labeling when human data are negative. We note that it is difficult to be certain that a lack of findings equates to a lack of risk because the failure of a study to detect an association between a drug exposure and an adverse outcome may be related to

many factors, including a true lack of an association between exposure and outcome, a study of the wrong population, failure to collect or analyze the right data endpoints, and/or inadequate power. The intent of this final rule is to require accurate descriptions of available data and facilitate the determination of whether the data demonstrate potential associations between drug exposure and an increased risk for developmental toxicities.

FDA proposed that when there are available human data that are not sufficient to use one of the risk conclusions for sufficient human data, the likelihood that the drug increases the risk of developmental abnormalities must be characterized as low, moderate, or high (proposed § 201.57(c)(9)(i)(C)(2)(ii)). In the preamble to the proposed rule, FDA sought comment on this subsection. Specifically, FDA sought "comment on whether, in situations with human data that are not sufficient, rather than classifying the risk as low, moderate, or high, the risk should instead be characterized by specific statements describing the findings, or whether the findings should be described at all if they are not readily interpretable. Examples of specific statements would be: 'Limited data in humans show (describe outcomes),' or 'Limited data in humans show conflicting results (describe study types, number of cases, outcomes, and limitations)'" (73 FR 30831 at 30842).

(Comment 38) FDA received 10 comments from a variety of sources expressing strong disagreement with the proposal to use the terms "low," "moderate," and "high" to characterize the likelihood of increased risk of adverse outcomes due to drug exposure based on less than sufficient human data. FDA received only one comment supporting the proposal.

Four comments stated that the proposal to classify risk as low, moderate, or high based on insufficient human data might produce the same confusion as the current pregnancy category system. These comments explained that, as with the A, B, C, D, X category system, the use of

the categories low, moderate, and high to characterize the likelihood of increased risk of adverse outcomes would oversimplify the data and lump drugs with various types and amounts of data together without describing the basis for the conclusions. Another comment suggested that these characterizations are subjective and would be confusing to health care providers.

One comment recommended that when the human data are insufficient, FDA require the inclusion of the following risk conclusion: "Insufficient data--risk conclusion not established." Another comment recommended that FDA consider adopting something similar to the EMA's system. One comment suggested that the "Risk Summary" should include information about the findings, such as the gestational age of exposure, the target organ or organ system, and the findings should be characterized in terms of structural, developmental, growth, or functional abnormality. Another comment recommended that when the human data are not sufficient, the labeling contain statements specific to the findings rather than classifying the risk as low, moderate, or high. One comment suggested that when there are insufficient data, the labeling should include a statement explaining that it is not possible to draw conclusions based on insufficient human data. This comment also expressed a preference for referring to the data portion of the labeling rather than including a more detailed narrative discussion of insufficient human data in the fetal risk summary.

(Response) As discussed previously, FDA agrees that the term "sufficient human data" is ambiguous and we have removed the term from the final rule, as well as the distinction between "sufficient human data" and "other human data." FDA also agrees that the terms "low," "moderate," and "high" are subjective and should not be used to describe human data that cannot support a statement about fetal risk. The final rule requires instead that when human data are available that establish the presence or absence of any adverse developmental outcome(s)

associated with maternal use of the drug, the labeling must summarize the specific developmental outcome; its incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. As discussed earlier, the final rule also requires that if the 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 the disease or condition for which the drug is indicated, then the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population. The final rule also requires that the "Risk Summary" state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

Narrative description of risk(s) based on human data. FDA proposed that when there are human data, the risk conclusion must be followed by a brief description of the risks of developmental abnormalities as well as other relevant risks associated with the drug. To the extent possible, this description must include the specific developmental abnormality (e.g., neural tube defects); the incidence, seriousness, reversibility, and correctability of the abnormality; and the effect on the risk of dose, duration of exposure, and gestational timing of exposure. When appropriate, the description must include the risk above the background risk attributed to drug exposure and confidence limits and power calculations to establish the statistical power of the study to identify or rule out a specified level of risk (proposed § 201.57(c)(9)(i)(C)(4)).

In the final rule, FDA has removed the "Narrative description of risk(s)" heading from the "Pregnancy" subsection. FDA has determined that much of the information required under that heading by the proposed rule was duplicative of information now required in the "Risk Summary." As discussed previously, when human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the "Risk Summary" in the "Pregnancy" subsection must summarize the specific developmental outcome; its incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. Because this information is required to be included in a narrative form in the "Risk Summary," we determined that including a separate "Narrative description of risk(s)" heading in the labeling was unnecessary. In addition, as explained in the following comments and our responses, some of the information that was required by the proposed rule to appear under "Narrative description of risk(s)" is required by the final rule to appear instead under "Clinical Considerations."

(Comment 39) One comment suggested that FDA add a statement to the "Narrative description of risk(s)" portion of the "Pregnancy" subsection of labeling that explains that spontaneous abortions caused by a drug could potentially mask the risk of developmental abnormalities.

(Response) Although FDA acknowledges that embryo-fetal death (i.e., spontaneous abortion) does sometimes occur due to severe developmental abnormalities, the Agency has determined that it is not necessary to explicitly include such a statement in labeling. Any increase in spontaneous abortions attributed to drug exposure above the background risk is required to be described in the "Risk Summary."

(Comment 40) One comment stated that the term "seriousness" is ambiguous and suggested replacing it with the phrase "impact on health." Two comments requested clarification of the terms "reversibility" and "correctability."

(Response) FDA agrees that the term "seriousness" is not clear, and it is not used in the final rule; it has been replaced with a requirement that the labeling describe the potential severity of the adverse reaction. Information about the reversibility of adverse reactions should be included under the heading, "Fetal/Neonatal adverse reactions," under "Clinical Considerations." This portion of the final rule requires that 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, the labeling must describe the adverse reaction, the potential severity and reversibility of the adverse reaction, and available interventions for monitoring or mitigating the reaction.

In response to the comments requesting clarification of the terms "reversibility" and "correctability," FDA considers a condition to be reversible if it can self-correct with routine care and nurturing or through an intervention such as discontinuing the drug. An example of a potentially reversible drug effect in the neonate is provided in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with the final rule. The term "correctable" has been removed from the final rule.

(Comment 41) One comment suggested that FDA include in the "Narrative description of risk(s)" information about precautionary measures that can be taken to prevent an adverse outcome caused by the drug.

(Response) FDA agrees that information about precautionary measures to prevent an adverse drug effect should be included in labeling. In the final rule, under "8.1 Pregnancy," "Clinical Considerations," "Maternal adverse reactions," FDA requires that if the use of the drug

is associated with a maternal adverse reaction that is unique to pregnancy or if a known adverse reaction occurs with increased frequency or severity in pregnant women, the labeling must describe the adverse reaction and available intervention(s) for monitoring or mitigating it. Also, in the final rule, FDA requires that under "8.1 Pregnancy," "Clinical Considerations," "Fetal/Neonatal adverse reactions," 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, the labeling must describe the adverse reaction, the potential severity and reversibility of the adverse reaction, and available intervention(s) for monitoring or mitigating the reaction. For further discussion of these requirements, see Comment 61 and our response.

(Comment 42) One comment suggested that FDA replace the phrase "risk attributed to drug exposure" in the "Narrative description of risk(s)" with the phrase "a drug's potential to contribute to the risk of adverse outcomes."

(Response) As discussed previously, the "Narrative description of risk(s)" heading was removed from the final rule, and the phrase "risk attributed to drug exposure" is not used elsewhere in the final rule.

(Comment 43) Two comments stated that confidence intervals and power calculations should not be included in labeling because they are too technical and not useful for most prescribers.

(Response) FDA does not agree. Under "Data," the final rule requires a description of the limitations of any data included in the labeling. Confidence intervals and power calculations are important for the review and interpretation of the data. As noted in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with the final rule, the confidence intervals and power calculation, when available, should be part of that description of

limitations.

(Comment 44) One comment suggested that the "Narrative description of risk(s)" include a discussion about the uncertainties or limitations of the "Fetal Risk Summary" when appropriate.

(Response) As discussed previously, FDA has removed the "Narrative description of risk(s)" heading from the final rule. In the final rule, any uncertainties or limitations of the data are required to be stated in "Data."

(Comment 45) One comment suggested that the "Narrative description of risk(s)" cross-reference "Data" to direct readers to the information upon which the narrative is based.

(Response) As discussed previously, the "Narrative description of risk(s)" was removed from the final rule.

Risk statement based on animal data. FDA proposed to require that when the data on which the risk conclusion is based are animal data, the "Fetal Risk Summary" must characterize the likelihood that the drug increases the risk of developmental abnormalities using one of the following risk conclusions: Not predicted to increase the risk, low likelihood of increased risk, moderate likelihood of increased risk, high likelihood of increased risk, or insufficient data (proposed § 201.57(c)(9)(i)(C)(3)(i)-(c)(9)(i)(C)(3)(v)). In the preamble to the proposed rule, the Agency sought comment on whether these standardized statements can adequately communicate different levels of risk based on animal data and their potential relevance to human fetal effects or whether these statements are likely to generate confusion among prescribers (73 FR 30831 at 30843).

(Comment 46) Comments expressed different opinions about the proposal to use standardized statements to characterize animal data. FDA received 11 comments, primarily from

toxicologists, teratologists, and organizations representing toxicologists and teratologists, as well as a few comments from drug manufacturers, expressing strong disagreement with the proposal to use risk statements to characterize animal data. FDA received three comments that supported using standardized statements to characterize the likelihood, based on animal data, that a drug will increase the risk for a known developmental abnormality. These comments explained, for example, that a standardized statement indicating the possible correlation between animal and human data would be helpful to clinicians.

Two comments stated that the proposed categories are confusing and subject to variable interpretation. One of these comments explained that it will be very difficult to categorize the results of multiple studies conducted for a single drug into one of the proposed categories, and there could be disagreement about whether to characterize the risk based on the animal data as "low," "moderate," or "high."

Several comments stated that the proposal to use category language to describe animal data demonstrates a misunderstanding of the function and meaning of experimental animal studies. These comments explained that although animal data can identify the potential of a therapeutic agent to cause developmental toxicity, it cannot give rise to an estimate of the probability of human harm.

Two comments expressed concern that the use of standardized risk statements would amount to a category system similar to the one that FDA currently uses and would have all of its associated problems.

Several comments expressed particular concern with the proposal to use these categories without an accompanying narrative description of the animal studies. One comment suggested that the sample labels provided in the Appendix of the proposed rule illustrate the difficulty of

trying to characterize the risk to humans based on animal data. Another comment stated that "the terms 'risk,' 'medium,' and 'high' are highly charged terms" and expressed concern that the risk statements will be over-interpreted by anxious consumers and their clinicians.

One comment suggested that rather than using the proposed risk statements, FDA should instead use the standardized statements presented in the draft reviewer guidance on "Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities" (October 2001).

Most of the comments that disagreed with the proposed standardized risk statements suggested that the labeling instead contain narrative statements describing the animal data and its potential relationship to human pregnancy risk. One of these comments explained that "succinct narrative statements will promote a reasoned risk assessment, facilitate comparisons among drugs, and enhance risk communication." Several of these comments suggested that the labeling should describe animal data qualitatively, including the number of species with positive findings, consistency of findings, and the type of findings.

(Response) The Agency has determined that the terms "not predicted to increase the risk," "low likelihood of increased risk," "moderate likelihood of increased risk," and "high likelihood of increased risk" are confusing and subject to different interpretations. The Agency believes that using standardized risk statements may give the false impression that animal data can provide a semi-quantitative assessment of human risk. The Agency also agrees that the use of standardized risk statements to characterize the risk of developmental abnormalities based on animal data would potentially have the same drawbacks as the current pregnancy category system. Therefore, in the final rule, FDA removed the requirement that a standardized risk statement be used to describe human risk based on animal data. Instead, the "Risk Summary"

requires that when animal data are available, the labeling must summarize the findings in animals and, based on these findings, describe, for the drug, the potential risk of adverse developmental outcomes in humans. The final rule requires that the statement include the number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human exposure or dose equivalents, and outcomes for pregnant animals and offspring. The final rule also requires that when animal studies do not meet current standards for nonclinical developmental toxicity studies or when there are no animal data, the labeling must so state.

(Comment 47) Two comments suggested that labeling should include language explaining the limitations of using animal data to predict the likelihood that the drug increases the risk of developmental abnormalities.

(Response) FDA declines the suggestion to include language in labeling explaining the limitations of using animal data to predict the likelihood that the drug increases the risk of developmental abnormalities, because this is beyond the scope of this rule, and is discussed in guidance documents, such as FDA's guidance for industry on "Reproductive and Developmental Toxicities--Integrating Study Results to Assess Concerns" (September 2011).

(Comment 48) FDA proposed that the "Risk Summary" contain "risk conclusions" based on animal data. One comment suggested that the term "risk conclusion" be replaced with the term "risk statement" because it is difficult to reach any conclusions about fetal risk posed by drugs based solely on animal data.

(Response) FDA agrees. As with human data, in the final rule, the Agency has replaced the term "risk conclusion" with the term "risk statement" when discussing risks based on animal data.

(Comment 49) Risk statement based on pharmacology. One comment suggested that FDA consider whether a separate approach is appropriate for a group of drugs, such as oncology products, for which the pharmacological and toxicological mechanisms are similar. The comment suggested that for cytotoxic drugs, FDA could use the following standard risk statement: "(Drug name) is indicated for (cancer type) and is generally used in terminally ill patients. There are very limited data on exposure in pregnant patients and, therefore, no assessment of fetal or maternal risk is available. The mechanism of action of this drug is to kill growing cells and it can be anticipated that there is a risk to the fetus at all stages of development."

(Response) FDA agrees that the "Pregnancy" subsection of labeling should address situations in which a drug may result in an increased risk of adverse developmental outcomes based on a well-understood mechanism of action. The final rule requires that when the drug has a well-understood mechanism of action that may result in adverse developmental outcome(s), the "Risk Summary" must explain the mechanism of action and the potential associated risks.

Contraindications, warnings, and precautions. FDA proposed that the "Fetal Risk Summary" refer to information that is included in the "Contraindications" or "Warnings and Precautions" section of labeling regarding an increased risk to the fetus from exposure to the drug (proposed § 201.57(c)(9)(i)(C)(5)).

(Comment 50) One comment suggested that FDA specify that any contraindications or warnings or precautions that must be included in the "Fetal Risk Summary" are those that relate to risk to the fetus.

(Response) In the final rule, FDA removed the requirement that the "Risk Summary" refer to information that is included in the "Contraindications" or "Warnings and Precautions"

section of labeling regarding an increased risk to the fetus from exposure to the drug. As described in FDA's draft guidance for industry implementing the PLR, when a topic is discussed in more than one section of labeling, the section containing the most important information relevant to prescribing should typically include a succinct description and should cross-reference sections that contain additional detail (FDA's guidance for industry on "Labeling for Human Prescription Drug and Biological Products--Implementing the PLR Content and Format Requirements" (February 2013)). Consistent with that principle, cross-referencing of information required under the final rule will typically appear in the section where the topic is briefly summarized, e.g., "Warnings and Precautions," and will refer the reader to the place in labeling where it will be presented in greater detail, i.e., "Pregnancy." We note that because a contraindication is important information that needs to be communicated to the health care provider, the final rule requires that when use of a drug is contraindicated during pregnancy, this information must be stated first in the "Risk Summary."

iv. Clinical considerations.

FDA proposed that the "Pregnancy" subsection of prescription drug labeling include a "Clinical Considerations" component to provide guidance and information to health care providers about the use of the drug in three distinct clinical situations: (1) Counseling women who were inadvertently exposed to the drug during pregnancy, (2) making prescribing decisions for pregnant women, and (3) making prescribing decisions during labor and delivery (proposed § 201.57(c)(9)(i)(D)).

We received many comments on this proposal. Based on those comments, FDA has made some changes to the final rule. A description of each comment we received and our responses follow.

(Comment 51) General comments. Comments expressed different opinions about the utility and appropriateness of the proposed "Clinical Considerations" component. Many comments expressed general support for including this information. One comment stated that "Clinical Considerations" will help clinicians and patients to consider all aspects of the patient's care when deciding when and how to prescribe drugs during pregnancy and in women of childbearing potential. Another comment stated that the title "Clinical Considerations" encourages professionals to make their own medical judgments. A separate comment noted that FDA refrained from interfering with the physician's discretion by framing "Clinical Considerations" as a practical guide that assists the provider in decisionmaking.

Some comments cautioned that "Clinical Considerations" was too directive in its advice and requiring this information intruded on the practice of medicine and could increase physician liability for failure to adhere to labeling instructions. One comment stated that "Clinical Considerations" should not dictate prescribing by a physician for pregnant women. The comment requested that FDA revisit this provision to see whether the content can be made more useful without advising physicians how to practice medicine. In particular, the comment suggested that information about known alternative therapies should be included. Alternatively, the comment suggested that FDA consider the use of a general statement about clinical considerations rather than an extensive, clinically based discussion that may be unable to incorporate risk and benefit information. Another comment stated that it is the health care provider's responsibility to keep abreast of the latest information about the disease state and its effect on pregnant women and to apply that knowledge to treatment of each individual patient, and the professional labeling is not the appropriate place for this information.

(Response) FDA disagrees both that "Clinical Considerations" is too directive and that professional labeling is not the appropriate place for this information. As a Public Health Agency with expertise in drug regulation and safety, FDA has a responsibility to issue regulations that facilitate the development of drug labeling that communicates how to safely and effectively prescribe drugs in the clinical setting. The Agency does not regard "Clinical Considerations" as dictating prescribing decisions. Rather, FDA views the "Clinical Considerations" component of "Pregnancy" as providing information that supports health care providers' understanding of drug product risks and benefits and facilitates informed prescribing decisions and patient counseling.

Inadvertent exposure. FDA proposed that under the subheading "Clinical Considerations," the "Pregnancy" subsection of labeling include information regarding known or predicted risks to the fetus from inadvertent exposure to the drug during pregnancy (proposed § 201.57(c)(9)(i)(D)(1)). The proposed rule would have required that: The labeling must discuss the known or predicted risks to the fetus from inadvertent exposure to the drug (exposure in early pregnancy before a woman knows she is pregnant), including human or animal data on dose, timing, and duration of exposure. If there are no human or animal data to assess the risk from inadvertent exposure, the labeling must so state.

(Comment 52) Comments expressed different opinions about the necessity and utility of including this information.

Two comments supported including information about inadvertent exposure. One of these comments explained that the proposed section improves a physician's ability to manage such cases.

Two comments, however, suggested that FDA consider removing this requirement because it will be duplicative of the information contained in the "Fetal Risk Summary." One of these comments explained that assuming equal exposure to the drug, the known or predicted risks to the fetus would be the same regardless of whether the exposure was intentional or not. This comment explained that because fetal risks are already fully described in the "Fetal Risk Summary," including the same information under "inadvertent exposure during pregnancy" would be redundant. The comment suggested that the "inadvertent exposure during pregnancy" component instead include a cross-reference to the "Fetal Risk Summary" and describe only information not already described in the "Fetal Risk Summary," in particular, any information about ways to manage or mitigate the effects of inadvertent drug exposure. The other comment explained that the risk of drug exposure to the fetus early in pregnancy should not be different between women who choose to become pregnant and those whose pregnancies were unplanned.

Another comment suggested that FDA either delete the statement "exposure in early pregnancy before a woman knows that she is pregnant" or retain it as an example. This comment explained that although inadvertent exposure is more likely in early pregnancy, it may occur at any time during pregnancy.

One comment asked for clarification as to what is expected to be included in this section. Specifically, this comment questioned how the risk conclusions from animal data in the "Fetal Risk Summary" will be used to counsel clinicians on the risk of inadvertent exposure, and requested that FDA provide examples of this section in an Appendix.

(Response) The Agency agrees that the proposed "inadvertent exposure during pregnancy" component would have required information about drug effects on the fetus that is largely redundant of the information that is required to be included in the "Risk Summary" in the

"Pregnancy" subsection of prescription drug labeling. FDA has removed the "inadvertent exposure during pregnancy" component from the final rule.

Prescribing decisions for pregnant women. FDA proposed that the "Clinical Considerations" portion of the "Pregnancy" subsection of prescription drug labeling contain information about prescribing decisions for pregnant women, including the following: (1) The risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat; (2) information about dosing adjustments during pregnancy; (3) information about maternal adverse reactions associated with use of the drug; and (4) information about any known or anticipated complications in the neonate from treatment of the pregnant woman (proposed § 201.57(c)(9)(i)(D)(2)).

In the final rule, FDA removed the heading "Prescribing decisions for pregnant women." FDA determined that because the "inadvertent exposure" component was removed from the final rule, the "Clinical Considerations" portion of the "Pregnancy" subsection was shortened such that having a separate heading for "Prescribing decisions for pregnant women" was unnecessary.

FDA received comments about the information required in the proposed rule under the heading "Prescribing decisions for pregnant women." A description of each comment and our responses follow.

FDA proposed that the "Prescribing decisions for pregnant women" component under "Clinical Considerations" include information about the risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat (proposed § 201.57(c)(9)(i)(D)(2)(i)).

(Comment 53) Comments disagreed about whether the "Pregnancy" subsection of labeling should include information about the effects of not treating the woman's underlying disease or condition.

Two comments supported requiring the inclusion of information about the short- and long-term effects of not taking a necessary drug to treat a chronic disease or condition for the duration of a pregnancy, as well as information about the severity of the condition for which the drug might be prescribed.

Two other comments, however, disagreed with including information in "Clinical Considerations" about the risks of not treating the mother's underlying disease or condition during pregnancy. These comments stated that prescription drug labeling is not the appropriate place for health care providers to learn about the risks of diseases that drugs are indicated to treat.

(Response) FDA has determined that when relevant information is available about the serious effects of not treating conditions or diseases during pregnancy, it must be included in this section of labeling. In the final rule, this requirement appears first under "Clinical Considerations" under the heading "Disease-associated maternal and/or embryo/fetal risk." The wording of this portion of the final rule was revised to require that when there is a 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 to be used, the labeling must describe the risk.

(Comment 54) Other comments suggested that the "Clinical Considerations" component of the proposed rule be altered in various ways.

Two comments expressed concern that descriptions of risks to the pregnant patient or fetus posed by diseases or conditions would vary among drugs that are indicated to treat the same

disease or condition, thereby promoting confusion. One of these comments suggested that FDA develop disease-specific text for developmental risks of major disease classes, such as asthma, hypertension, diabetes, and epilepsy, which sponsors can use in their prescription drug labeling. This comment also requested that the information be updated on a timely basis.

(Response) FDA agrees that it is important that information provided in labeling is consistent and up-to-date, and we address this issue in our response to Comment 4. FDA is not mandating that labeling contain consistent disease-specific text, as knowledge of disease-associated risk may change over time as more data become available.

(Comment 55) One comment suggested that FDA add a statement under "Clinical Considerations" explicitly stating that untreated or inadequately treated health conditions (such as infections; chronic diseases such as diabetes, hypertension, renal and thyroid diseases; and psychiatric disorders such as depression) can adversely affect the health of the woman and the outcomes of the pregnancy, and that decisions about medication usage must be balanced with the risks of untreated and/or poorly managed health conditions.

(Response) FDA disagrees with this suggestion. We have determined that requiring a general standardized statement is less effective than providing drug-specific information about the risks of not treating the condition or disease for which the drug is indicated to be used.

(Comment 56) One comment suggested that "Clinical Considerations" should provide information about how to discontinue or switch medications during pregnancy when necessary.

(Response) FDA agrees that when such information is available, it may be appropriate to include it in "Clinical Considerations." We note that this does not require a change to the final rule, because this is consistent with current labeling practices.

(Comment 57) One comment suggested that "Clinical Considerations" take into account the severity of the disease, disorder, or condition to the mother, and the availability and the benefits and risks of alternative therapies for which greater or lesser knowledge may be known about their use in pregnant women.

(Response) FDA disagrees with the suggestion that the labeling address the availability and the benefits and risks of alternative therapies during pregnancy. Because the comparative risks and benefits for different therapies may vary by patient, this determination must be made by the prescribing health care provider. FDA acknowledges, however, that under certain circumstances it may be appropriate to include a statement in the labeling that pregnant women should consider alternative drug therapies, and the appropriateness of this would be evaluated on a case-by-case basis during the labeling review process for a specific application.

Dosing adjustments during pregnancy. FDA proposed that "Clinical Considerations" provide information about dosing adjustments during pregnancy (proposed § 201.57(c)(9)(i)(D)(2)(ii)). The proposed rule stated that this information must also be included in the "Dosage and Administration" and "Clinical Pharmacology" sections of the labeling, and that if there are no data on dosing during pregnancy, the labeling must so state.

(Comment 58) One comment suggested that dosing information should be restricted to the "Dosage and Administration" section of labeling and that "Clinical Considerations" should cross-reference the "Dosage and Administration" and "Clinical Pharmacology" sections of the labeling rather than repeat dosing adjustment information in the "Pregnancy" subsection of labeling. The comment also suggested replacing the phrase "no data" because it could become outdated and because, in some instances, there may be data but it might not be sufficient to support recommendations for dosing adjustments.

(Response) We disagree with the suggestion that all information about dosing should be restricted to the "Dosage and Administration" section of labeling. FDA has determined that it is important that labeling information relevant to the use of the drug during pregnancy be included in the "Pregnancy" subsection. These issues are discussed in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with the final rule. If there are pharmacokinetic data that support dose adjustment(s) during pregnancy and the postpartum period, this information must be provided under the heading, "Dose adjustments during pregnancy and the postpartum period" in "Clinical Considerations," and there should be a cross-reference to other sections of labeling that include more details (e.g., "Dosage and Administration" or "Clinical Pharmacology"). Although in the proposed rule FDA had required a cross-reference to "Dosage and Administration" and "Clinical Pharmacology," we have removed that requirement. We believe, however, that when appropriate, a cross-reference should be included. This approach is consistent with the regulations and guidance applicable to the "Dosage and Administration" section of labeling (§ 201.57(c)(3)) and FDA's guidance for industry on "Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products--Content and Format" (March 2012), which require that the labeling provide details on how to adjust or modify the dosage in the "Dosage and Administration" section of labeling, including for specific patient populations.

FDA agrees with the suggestion to remove the phrase "no data" from the final rule. In the final rule, we have removed the requirement to state if there are no data available on dose adjustments during pregnancy and the postpartum period. In addition, as noted in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with the final rule, headings under "Clinical Considerations" (including "Dose adjustments during

pregnancy and the postpartum period") should be omitted if there are no data available or the available data are not relevant.

Maternal adverse reactions. FDA proposed that "Clinical Considerations" contain information about maternal adverse reactions that are unique to pregnancy or adverse reactions that occur with increased frequency or severity in pregnant women. The proposed rule required that the labeling also describe any interventions that may be needed, such as monitoring blood glucose for a drug that causes hyperglycemia in pregnancy (proposed § 201.57(c)(9)(i)(D)(2)(iii)).

(Comment 59) One comment suggested that a cross-reference, "see Pregnancy," be added to the "Adverse Reactions" section of labeling to ensure that health care providers refer to this section.

(Response) FDA disagrees with this comment. The conventions for cross-referencing are explained in FDA's guidance for industry on "Labeling for Human Prescription Drug and Biological Products--Implementing the PLR Content and Format Requirements" (February 2013). The suggestion that this rule require a cross-reference from the "Adverse Reactions" section to the "Pregnancy" subsection of labeling is not consistent with the conventions set forth in that guidance. In addition, not every drug product will have pregnancy-related adverse reactions; thus, a required cross-reference is unnecessary.

(Comment 60) One comment suggested that "Clinical Considerations" refer to "available" interventions rather than "needed" interventions to avoid interfering with the practice of medicine.

(Response) FDA agrees with the suggestion to replace the phrase "interventions that may be needed" with the phrase "available interventions." In the final rule, FDA requires that if use

of the drug is associated with a maternal adverse reaction that is unique to pregnancy or if a known adverse reaction occurs with increased frequency or severity in pregnant women, the labeling must describe the adverse reaction and available intervention(s) for monitoring or mitigating the reaction. This change also allows for differences that may exist in community standards of care and available services across the United States. We note that in the final rule we removed the following language from the codified: "e.g., monitoring blood glucose for a drug that causes hyperglycemia in pregnancy."

Fetal/Neonatal adverse reactions. FDA proposed that "Clinical Considerations" contain information about any known or anticipated complications in the neonate, including any interventions that might be needed (proposed § 201.57(c)(9)(i)(D)(2)(iv)).

(Comment 61) Two comments asked FDA to clarify the meaning of the term "complication." One comment suggested that if FDA intended the term "complication" to mean adverse reaction in the neonate, the Agency should use the term "adverse reaction." This comment also suggested that if an adverse reaction/complication has been described in the "Fetal Risk Summary," only a cross-reference to § 201.57(c)(9)(i)(C) should be required to appear in § 201.57(c)(9)(i)(D)(2)(iv). Another comment suggested that FDA state that a "complication" could be an "adverse drug reaction," and suggested that FDA state that the term "adverse drug reaction" may be used when appropriate.

(Response) FDA agrees that "adverse reaction" is a more appropriate term and that it is more consistent with the other portions of the final rule. In the final rule, the term "adverse reaction" (as defined in § 201.57(b)(7)) has replaced "complication." Additionally, in the final rule FDA is requiring the inclusion of information regarding fetal adverse reactions in this section of labeling. Although the proposed rule only addressed adverse reactions (referred to

there as "complications") in the neonate under what in the final rule is required in § 201.57(c)(9)(i)(C), FDA concludes that information intended to inform prescribing decisions for pregnant women appropriately includes information on fetal adverse reactions as well as neonatal adverse reactions. FDA does not believe that there is a principled distinction between the importance of such information with respect to the fetus and with respect to the neonate. The consistent location under "Clinical Considerations" of information about potential adverse reactions in the fetus as well as in the pregnant woman and the neonate, and about available interventions, will make the information in that subsection more useful, as well as easier to identify for prescribers and other health care providers. Accordingly, the final rule requires that if it is known or anticipated that maternal drug therapy increases the risk of an adverse reaction in the fetus or the neonate, the labeling must describe the adverse reaction, the potential severity and reversibility of the adverse reaction, and available intervention(s) for monitoring or mitigating the reaction.

FDA disagrees with the suggestion that if an adverse reaction/complication has been described in the "Fetal Risk Summary," only a cross-reference to § 201.57(c)(9)(i)(C) should be required to appear in § 201.57(c)(9)(i)(D)(2)(iv). As discussed in the draft guidance on pregnancy and lactation labeling, which is being published concurrently with the final rule, the "Clinical Considerations" portion of the labeling is intended to describe fetal/neonatal adverse reactions that are not adverse developmental outcomes. Therefore, because the two portions of the labeling address different potential reactions/outcomes, a cross-reference would not be appropriate.

Additionally, in the final rule, FDA added the requirement that the labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk of an adverse

reaction in the fetus or neonate as FDA has concluded that this information is important for informing prescribing decisions.

Drug effects during labor or delivery. FDA proposed that the "Clinical Considerations" portion of pregnancy labeling contain information about drug effects during labor or delivery for drugs that have a recognized use during labor or delivery, whether or not the use is stated as an indication in the labeling, or are expected to affect labor or delivery (proposed § 201.57(c)(9)(i)(D)(3)).

(Comment 62) One comment supported the proposal to merge information about labor and delivery into the "Pregnancy" subsection of labeling.

Another comment expressed concern that including information about drugs used during labor or delivery, including drugs that are used off-label during labor or delivery, conflicts with FDA's long-standing position that off-label information is not to be included in labeling.

(Response) We note that, as stated in the proposed rule (73 FR 30831 at 30844), the language proposed for this heading contained only slight modifications from that in existing § 201.57(c)(9)(ii). However, because important safety information, whether for an approved or unapproved use, may be required to be included in labeling (see, e.g., § 201.57(c)(6)(i)), we concluded that it is not necessary to include specific language regarding this issue. Therefore, FDA has removed the language regarding "drugs that have a recognized use during labor or delivery, whether or not the use is stated as an indication in the labeling." In the final rule, FDA revised the heading "Drug effects during labor or delivery" to "Labor or delivery," which is consistent with the level of specificity used in the other headings under "Clinical Considerations."

v. Data.

FDA proposed that the following information be included in the "Pregnancy" subsection of labeling under the subheading "Data":

(1) Under the subheading "Data," the "Pregnancy" subsection of the labeling must provide an overview of the data that were the basis for the fetal risk summary.

(2) Human and animal data must be presented separately, and human data must be presented first.

(3) The labeling must describe the studies, including study type(s) (e.g., controlled clinical or nonclinical, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies), animal species used, exposure information (e.g., dose, duration, timing), if known, and the nature of any identified fetal developmental abnormalities or other adverse effect(s). Animal doses must be described in terms of human dose equivalents and the basis for those calculations must be included.

(4) For human data, positive and negative experiences during pregnancy, including developmental abnormalities, must be described. To the extent applicable, the description must include the number of subjects and the duration of the study.

(5) For animal data, the relationship of the exposure and mechanism of action in the animal species to the anticipated exposure and mechanism of action in humans must be described. If this relationship is not known, that should be stated (proposed § 201.57(c)(9)(i)(E)).

FDA received comments about the information required under "Data" in the proposed rule and made some changes to the final rule. The following discussion addresses these comments, our responses, and the changes to the final rule.

(Comment 63) References. One comment suggested that under "Data," the labeling should include references for the cited data. The comment explained that including references for the data would allow clinicians and other health care workers to further research pregnancy issues.

(Response) We decline this suggestion. FDA has determined that prescription drug labeling is intended to facilitate prescribing decisions and is not intended as a research tool. We also note that this final rule is a part of labeling regulations, found at § 201.57, which address the inclusion of references in prescription drug labeling (see § 201.57(c)(16)).

(Comment 64) Postmarketing reporting of adverse reactions. One comment stated that if specific numbers of adverse event reports are included in drug labeling, the labeling will need to be constantly updated. The comment suggested that the Agency instead consider using quantitative measures of frequency to produce a more stable label.

(Response) FDA acknowledges that the inclusion in labeling of actual numbers of postmarketing reports for particular adverse reactions is often not appropriate. We agree that the number of postmarketing reports of adverse reactions changes over time and labeling may become rapidly outdated. In addition, postmarketing reports of adverse reactions generally do not establish an incidence or prevalence of a particular outcome or definitively demonstrate an association between prenatal exposure to the drug in question and the adverse developmental outcome. However, FDA also recognizes that there may be isolated situations in which reporting of adverse reactions corroborates other human data and, in these situations, it may be appropriate to list a specific number of cases with the date when the reporting was collected. FDA will consider whether the labeling for a drug product should include specific numbers of reports of

adverse reactions on a case-by-case basis based on evaluating all available data and principles of epidemiology and data interpretation.

In the final rule, FDA replaced the phrase "provide an overview of the data" with "describe the data." FDA made this change to clarify our intention that under the subheading "Data," the labeling must include a more detailed description of the data than might be understood from use of the term "overview." In the final rule, FDA also added the requirement that under "Data," the labeling describe the data that are the basis for the "Clinical Considerations." The proposed rule stated that "Data" must describe the data that were the basis for the fetal risk summary, and did not address the data that were the basis for "Clinical Considerations." FDA has determined that there is no principled reason to distinguish between the data under the fetal risk summary and that underlying "Clinical Considerations." Accordingly, the final rule requires that under the subheading "Data," the labeling describe the data that are the basis for both the "Risk Summary" and "Clinical Considerations." This subheading, therefore, is only required to the extent that there are data that are the basis for these two subheadings and the headings under them.

FDA has also determined that the information in labeling would be clearer if human data and animal data appeared separately under applicable headings. In the final rule, FDA requires that human and animal data be presented separately under the headings "Human Data" and "Animal Data."

In the final rule, FDA requires that for human data, the labeling must describe adverse developmental outcomes, adverse reactions, and other adverse effects. To the extent applicable, the labeling must describe the types of studies or reports, number of subjects and the duration of each study, exposure information, and limitations of the data. The final rule requires that both

positive and negative study findings be included. The proposed rule listed various types of studies. These were removed from the final rule because we determined that it is more appropriate to discuss these elements in guidance.

Animal data. FDA proposed that human and animal data must be presented separately, and human data must be presented first.

(Comment 65) One comment suggested that FDA omit the requirement that human data must be presented first. The comment explained that the most robust data should be presented first regardless of whether it is animal or human data.

(Response) FDA declines this suggestion. We have determined that to promote consistency and to meet readers' expectations that information will always be found in the same place, a fixed order of presentation must be maintained. Additionally, as discussed in the preamble to the proposed rule, the importance of human data in labeling was stressed by physicians who participated in focus group testing of the model labeling format and also by the FDA advisory committee that provided input on the proposed format (73 FR 30831 at 30841). FDA has determined that human data should always be presented first because human data are often the most relevant to prescribers, and animal data may not always be applicable to humans.

FDA also proposed that animal doses must be described in terms of human dose equivalents and the basis for those calculations must be included.

(Comment 66) Two comments suggested that the final rule remove the requirement to use "administered dose" as a comparator between animal and human data and to replace it with comparisons based on systemic exposure, if available. One of these comments explained that basing the comparison on systemic exposure will provide greater consistency within the labeling and will also provide a way to more easily make comparisons between drugs.

(Response) FDA declines this suggestion to restrict the comparison to only those based on systemic exposure. We agree that comparisons based on systemic exposure could provide consistency within labeling and therefore the final rule requires that they must be included when data are available, but the data are not always available for such a comparison. FDA believes that including the human dose equivalent may be more meaningful information for health care providers, particularly in the absence of data to make comparisons based on systemic exposure, and as such, in the final rule, a comparison of the animal to human doses must be included using the data available.

The proposed rule required that for animal data under the "Data" component the relationship of the exposure and mechanism of action in the animal species to the anticipated exposure and mechanism of action in humans be described. In the final rule, we removed this requirement because often this relationship is not known. The final rule requires that animal doses or exposures be described in terms of human dose or exposure equivalents, and that the basis for those calculations be included.

2. 8.2 Lactation

FDA proposed that the "Nursing mothers" subsection of prescription drug labeling be replaced with the subsection "Lactation" (proposed §§ 201.56(d)(1) and 201.57(c)(9)(ii)). FDA proposed that the "Lactation" subsection of prescription drug labeling contain the following subheadings: "Risk Summary," "Clinical Considerations," and "Data" (proposed § 201.57(c)(9)(ii)). FDA received many comments about the proposed "Lactation" subsection and made changes to the final rule based on these comments. The discussion that follows addresses these comments, our responses, and the changes FDA made to the final rule.

a. General comments.

i. Support for "Lactation" subsection

(Comment 67) FDA received many comments expressing support for the proposed "Lactation" subsection. One of these comments explained that it is essential for drug labeling "to carry 'best science' information that enables clinicians to efficiently and thoroughly review what is known about the drug and any reported health effects to the breast-fed infant." The comment stated that the proposed rule would facilitate more efficient consideration of the data.

(Response) We agree with these comments, and our final rule requires labeling to include a subsection on lactation with risk and benefit information related to breastfeeding and the breast-fed infant.

ii. Drug alternatives

(Comment 68) One comment suggested that a statement should be included that many drugs for which we may not have lactation data have a suitable alternative for which we do have data.

(Response) We decline to adopt this comment. We do not believe it would be appropriate to include this type of statement in labeling. Because the comparative risks and benefits will vary among individual patients, a health care provider, in consultation with his or her patient, is in the best position to determine whether there is a "suitable alternative" for a particular drug.

iii. Validating data

(Comment 69) One comment expressed concern about the potential for bias or omissions with respect to which data the sponsor includes and the risk statements the sponsor uses to

characterize such data. The comment encouraged FDA to employ all reasonable means to validate the sponsor's collection, evaluation, and subsequent conclusions regarding lactation data.

(Response) FDA agrees. FDA will review data available in literature and sponsor-submitted data used for developing the "Lactation" subsection of drug labeling. We note that this does not require a change to the final rule because FDA's normal review process for prescription drug labeling includes validating the applicant's collection, evaluation, and subsequent conclusions regarding data.

b. Risk summary

i. "Active metabolites"

(Comment 70) Two comments suggested that FDA revise the "Risk Summary" so that it explicitly refers to active metabolites of the drug, in addition to the drug itself.

(Response) FDA agrees with this comment. We also have determined that it is appropriate to include information about the effects of a drug and/or its active metabolite(s) not only in the "Risk Summary," but under other subheadings in the "Lactation" subsection of labeling. Therefore, the final rule has been revised to refer explicitly to drugs and/or their active metabolites.

ii. "Compatible with breastfeeding"

FDA proposed that under the subheading "Risk Summary," if, as described under § 201.57(c)(9)(ii)(A)(1) through (c)(9)(ii)(A)(3) of the section, the data demonstrate that the drug does not affect the quantity and/or quality of human milk and there is reasonable certainty either that the drug is not detectable in human milk or that the amount of drug consumed via breast milk will not adversely affect the breast-fed child, the labeling must state: The use of (name of drug) is compatible with breastfeeding. After this statement (if applicable), the risk summary

must summarize the drug's effect on milk production, what is known about the presence of the drug in human milk, and the effects on the breast-fed child (proposed § 201.57(c)(9)(ii)(A)).

(Comment 71) Two comments suggested that FDA eliminate the statement, "The use of (name of drug) is compatible with breastfeeding" from the "Lactation" subsection of the final rule. One of the comments explained that it will be difficult to determine whether a drug is compatible with breastfeeding with such definitive certainty, especially since the term "compatible" implies safety. Another comment suggested that in the final rule FDA should replace the statement "compatible with breastfeeding" with a standardized statement that "sufficient" human data exist to indicate that the drug does or does not adversely affect the breast-fed child, followed by a supportive narrative.

(Response) FDA agrees that the term "compatible" is not clearly defined and implies that the use of a drug during lactation is "safe." No drug is completely safe even in a person who is not pregnant or breastfeeding. In addition to offering potential therapeutic benefit(s), all drugs have potential side effects and risks involved with their use. The balance between those benefits and risks is taken into account not just at the approval stage, but also helps direct diagnostic and treatment recommendations for a particular patient in a particular clinical scenario. Accordingly, in the final rule FDA removed the statement "The use of (name of drug) is compatible with breastfeeding."

Breastfeeding offers significant health benefits to both the child and mother. Different drugs and/or their active metabolites pass into breast milk in different concentrations; they may or may not be orally bioavailable in the infant, and they may or may not result in significant adverse reactions in the short term or adverse outcomes in the long term. Often, all of the

potential risks related to drug treatment during lactation are not known even though the benefits of breastfeeding are known and substantial.

FDA declines the suggestion to include a standardized statement that "sufficient" human data exist to indicate that the drug does or does not adversely affect the breast-fed child, followed by a supportive narrative. However, the final rule requires that if the drug is absorbed systemically, the labeling must include, under "Risk Summary," available information, if relevant, on the known or predicted effects on the breast-fed child from exposure to the drug and/or its active metabolite(s), including systemic and/or local adverse reactions. If the available information is sufficient to determine that use of the drug is contraindicated during breastfeeding, this significant information is required at the beginning of the "Risk Summary." The "Risk Summary" must state when there are no data to assess the effects of the drug on the child.

FDA also revised the final rule to require that if studies demonstrate the presence of the 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 breast-fed child, then the "Risk Summary" must describe the disposition of the drug and/or its active metabolite(s). FDA added this requirement to the final rule to identify situations in which a drug and/or its active metabolite(s) are present in human milk but the breast-fed child does not have any systemic exposure because of degradation in the gastrointestinal tract.

iii. Not systemically absorbed

FDA proposed that if data demonstrate that a drug is not systemically absorbed, the fetal risk summary must contain only the following statement: (Name of drug) is not absorbed systemically from (part of body) and cannot be detected in the mother's blood. Therefore,

detectable amounts of (name of drug) will not be present in milk. Breastfeeding is not expected to result in fetal exposure to the drug (proposed § 201.57(c)(9)(ii)(A)).

(Comment 72) One comment suggested that the statement be revised to focus on the route of administration rather than on the part of the body where the drug is administered. The comment also suggested that the language "cannot be detected in blood" could be omitted because it is redundant with "not systemically absorbed."

(Response) FDA agrees with this comment and we removed the phrase "cannot be detected in blood" from the final rule.

We also agree with the suggestion to focus on the route of administration. FDA agrees that "part of the body" could be misconstrued and we have determined that the use of "route of administration" to describe how the drug enters the body is more consistent with labeling language that addresses dosing and administration. In the final rule, FDA has replaced "part of the body" with "route of administration."

(Comment 73) Another comment suggested revising the language "systemically absorbed" to "has a systemic effect" to include the action of biological products (vaccines) that are immune stimulants rather than chemicals that are absorbed.

(Response) FDA declines the suggestion to change the language "systemically absorbed" to "has a systemic effect." The terms "systemically absorbed" and "absorbed systemically" refer to the absorption of the drug or biological product from its site of administration into serum and/or other body tissues where the drug or biological product, including a vaccine, can reach its receptor or target cell and exert its pharmacological or immunological effect. A drug or biological product that is not systemically absorbed will not be excreted into human milk and, therefore, breastfeeding should not result in the child's exposure to the drug. In the final rule,

FDA has deleted the sentence, "Therefore, detectable amounts of (name of drug) will not be present in breast milk." The final rule also replaces the sentence, "Breastfeeding is not expected to result in fetal exposure to the drug" with "breastfeeding is not expected to result in exposure of the child to (name of drug)."

(Comment 74) Two comments noted that the term "fetal" was used improperly in this section of the proposed rule.

(Response) FDA agrees and has removed the term "fetal" from the "Lactation" subsection and replaced it with the term "child."

iv. Presence of drug in human milk

FDA proposed that under the heading "Presence of drug in human milk":

(1) The risk summary must describe the presence of the drug in human milk in one of the following ways: The drug is not detectable in human milk; the drug has been detected in human milk; the drug is predicted to be present in human milk; the drug is not predicted to be present in human milk; or the data are insufficient to know or predict whether the drug is present in human milk;

(2) If studies demonstrate that the drug is not detectable in human milk, the risk summary must state the limits of the assay used; and

(3) If the drug has been detected in human milk, the risk summary must give the concentration detected in milk in reference to a stated maternal dose (or, if the drug has been labeled for pediatric use, in reference to the labeled pediatric dose), an estimate of the amount of the drug consumed daily by the infant based on an average daily milk consumption of 150 milliliters per kilogram of infant weight per day, and an estimate of the [percentage] of the maternal dose excreted in human milk (proposed § 201.57(c)(9)(ii)(A)(2)(i)-(c)(9)(ii)(A)(2)(iii)).

We received comments about this portion of the "Lactation" subsection of the proposed rule. The discussion that follows addresses these comments, our responses, and the changes FDA made to this portion of the "Lactation" subsection of the final rule.

(Comment 75) Predicting whether drug is present in human milk. Several comments objected to the proposal that the "Risk Summary" state that the drug is "predicted" or "not predicted" to be present in human milk. One of these comments stated that avoiding predictions and relying instead on clinical data would better assist providers. Two comments suggested that the statements about whether the drug is predicted or not predicted to be present in human milk should be omitted because the other proposed descriptions effectively cover the range of potential options.

(Response) FDA agrees that the terms "predicted" and "not predicted" should not be used in the "Risk Summary," and that a description of available data, if relevant, on the presence of the drug and/or its active metabolite(s) in human milk should be used instead. In addition, FDA has determined that, in order to provide clarity in the "Risk Summary," in situations where there are no data to assess whether the drug and/or its active metabolite(s) are present in human milk, the "Risk Summary" must so state.

(Comment 76) Limits of the assay used. Two comments suggested omitting assay information if the presence of drug in milk is not detectable. The comments stated that assay information is overly technical and unfamiliar for many health care providers. In addition, the comments explained that it would be presumed that during its review of the data, the review division at FDA would consider the validity of studies, including the assay's reliability and sensitivity, before approving the inclusion in labeling of a statement that the drug is not detectable in human milk.

(Response) FDA declines this comment. We have determined that the limit of the assay is critical to understanding the amount of the drug and/or its active metabolite(s) that may or may not be present in human milk. We also believe that most health care providers are capable of interpreting this data when presented in labeling and that health care providers are familiar with the importance of assay limits for all types of laboratory testing. In the final rule, FDA has retained the requirement from the proposed rule that if studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the "Risk Summary" must state the limits of the assay used.

(Comment 77) Concentration of the drug detected in human milk. Two comments expressed support for FDA's proposal that the "Lactation" subsection of prescription drug labeling provide the concentration of the drug detected in human milk in reference to a stated adult or labeled pediatric dose. One of these comments suggested that the labeling should also include the milligrams per kilogram received per day and the percentage of the weight-equivalent therapeutic dose administered to the mother. This comment requested that the doses be presented according to infant age ranges when possible. A separate comment suggested providing a calculation of the estimated infant daily dose consumed as compared to available pediatric dosing rather than to maternal dosing, but added that clinicians may have difficulty interpreting the calculations.

One comment stated that the concentration of the drug detected in milk should not be made in reference to the maternal dose or the labeled pediatric dose. The comment explained that the concentration of a drug in milk may vary widely depending upon whether it reflects steady-state or a single dose, and could vary based on the timing between the ingestion of the drug and taking the sample. The comment suggested that an estimate of the amount of the drug

consumed daily by the infant could be made in reference to the maximum maternal daily dose or the maximum labeled pediatric dose and that "an estimate of the [percentage] of the maternal dose excreted in human milk" could be omitted.

One comment suggested that FDA standardize the approach to presenting drug concentrations in breast milk and stated that this would ensure that uniform data are presented by all manufacturers, allowing for easy comparisons between prescription products. The comment also suggested that FDA provide a guidance document highlighting the value of breast milk area under the curve (AUC) concentrations, explaining that providing standardized ways of calculating weight-normalized drug doses and average breast milk consumption could better guide manufacturers and help create a unified approach to describing drug concentrations in breast milk.

(Response) FDA addresses these issues in the draft guidance for industry on "Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling" (February 2005) (the draft guidance on clinical lactation studies).

FDA agrees that it would be helpful to clinicians to provide infant drug exposure dosing in milligrams per kilograms received per day so that a clinician may compare it to a labeled infant or pediatric dose if available. However, because of the technical considerations for calculating drug and/or active metabolite levels in milk, FDA is not requiring this in the final rule.

FDA has determined that the actual or calculated infant daily dose must be compared to the labeled infant or pediatric dose, when available, and to the maternal dose when pediatric dosing is not available. When infant or pediatric dosing is available for a drug and pediatric pharmacokinetic data are available for a drug and/or its active metabolite(s), these data provide

an effective way to estimate comparative exposure (and potentially comparative safety) of a breast-fed child versus a child receiving a drug therapeutically.

Although not required by the final rule, FDA agrees that data presented according to infant age groups could be useful given the changes in infant hepatic and renal function during the first few months of life, and infants' increasing ability with age to metabolize and clear drugs and/or their active metabolites. These data may not always be available, but when they are, their presentation stratified by age would be clinically relevant and should be included in labeling.

(Comment 78) "No data." One comment suggested removing the phrase "no data" from the "Risk Summary" in the "Lactation" subsection, because there are rarely no data for a drug.

(Response) FDA disagrees with the suggestion to remove the phrase "no data" from the "Risk Summary." Often, there are no lactation data (either human or animal) at the time of approval of NDAs and BLAs.

v. Effects on milk production and quality

FDA proposed that if the drug is absorbed systemically, the risk summary must describe the effect of the drug on the quality and quantity of milk, including milk composition, and the implications of these changes to the milk on the breast-fed child (proposed § 201.57(c)(9)(ii)(A)(1)).

(Comment 79) Several comments stated that it is seldom feasible to adequately study the effects of a drug on the quality and quantity of breast milk, and this information should only be provided when available. One comment explained that to be scientifically valid, such evaluation requires a study before, during, and after drug exposure. This comment explained that further complicating factors are substantial inter- and intra-individual variation and small study sample size.

One comment requested that FDA include information about the effects of the drug on the woman's milk supply and other issues that affect the process of breastfeeding. The comment stated that many women are advised against taking medications that affect milk supply while lactating but are not informed that this is the reason they should avoid these medications.

(Response) Although FDA agrees that it is not always possible to determine the effects of a drug and/or its active metabolite(s) on milk production, we have determined that when the relevant data are available, this information must be included in the labeling. In the final rule, FDA requires that the "Risk Summary" describe the effects of the drug and/or its active metabolite(s) on milk production, and if there are no data to assess the effects of the drug and/or its active metabolite(s) on milk production, the "Risk Summary" must so state.

With respect to milk quality and composition, there are currently no established standards or documented population variability for milk content. It is also not known how much change in various milk components would reduce the known benefits of breastfeeding relative to the risks of exposure to a drug and/or its active metabolite(s) through breast milk combined with any potential effects on milk composition and quality. Accordingly, in the final rule, FDA has removed the requirement that the "Risk Summary" describe the effect of the drug on the quality and composition of milk, and the implications of these changes to the milk on the breast-fed child.

vi. Sufficient data

(Comment 80) One comment noted that the proposed rule does not require sufficient data to reach conclusions in the "Risk Summary" in the "Lactation" subsection, and suggested that FDA discuss what constitutes sufficient data, as it does in the "Pregnancy" subsection.

(Response) As discussed previously, many comments disagreed with FDA's proposed use of the term "sufficient" in the "Pregnancy" subsection of labeling. The comments stated that the term was not clearly defined in the proposed rule, and suggested that it would be difficult to apply the term consistently across drug labeling. Based on FDA's consideration of these comments, the final rule does not refer to "sufficient" data in either the "Pregnancy" or the "Lactation" subsection.

vii. Risk and benefit statement

(Comment 81) FDA received seven comments noting that the proposed "Lactation" subsection did not require the inclusion in labeling of any information about the benefits of breastfeeding. Some of these comments recommended that FDA add such a statement to the final rule to prevent patients from unnecessarily foregoing or discontinuing breastfeeding.

(Response) FDA acknowledges that the proposed rule did not require the inclusion of information about the benefits of breastfeeding. The Agency has determined that the inclusion in the "Lactation" subsection of labeling of a risk and benefit statement will provide a useful framework for health care providers to use when making prescribing decisions for lactating patients. In the final rule, FDA requires that for drugs absorbed systemically, unless breastfeeding is contraindicated during drug therapy, a statement that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for the drug and any potential adverse effects on the breast-fed child from the drug or from the underlying maternal condition, must be included at the end of the "Risk Summary" in the "Lactation" subsection of labeling.

c. Clinical considerations.

FDA proposed that under the subheading "Clinical Considerations," the labeling must provide the following information to the extent it is available: (1) Information concerning ways to minimize the exposure of the breast-fed child to the drug, such as timing the dose relative to breastfeeding or pumping and discarding milk for a specified period; (2) information about potential drug effects in the breast-fed child that could be useful to caregivers, including recommendations for monitoring or responding to these effects; and (3) information about dosing adjustments during lactation. This information must also be included in the 'Dosage and Administration' and 'Clinical Pharmacology' sections (proposed § 201.57(c)(9)(ii)(B)(1)-(c)(9)(ii)(B)(3)). FDA received comments about the proposed "Clinical Considerations" subheading. The discussion that follows addresses these comments, our responses, and FDA's changes to the final rule.

i. Other therapies

In the proposed rule, FDA included sample labeling for several fictitious drugs. In the "Clinical Considerations" portion of the "Lactation" subsection, the ALPHAZINE sample stated that "Other medical therapies are available for treatment of maternal hypertension."

(Comment 82) Two comments disagreed with the inclusion of this statement. The comments explained that the statement is confusing because although no comparator data are presented, clinicians may infer that other drugs in the class are safe and effective.

(Response) We note that the language to which these comments refer was included in sample labeling included with the proposed rule, and not in the proposed rule itself. FDA included sample labeling with the proposed rule to serve as examples of how to apply the requirements of the proposed rule in different scenarios. We note that the final rule does not

include sample labeling. FDA agrees, however, that statements such as, "Other medical therapies are available for treatment of maternal hypertension," may be confusing, and should not be included in the "Pregnancy" or "Lactation" subsections of labeling.

ii. Minimizing exposure to the breast-fed child

(Comment 83) General comments. Four comments disagreed with the proposal to include information regarding minimizing exposure of the breast-fed child in the "Clinical Considerations" portion of the "Lactation" subsection. These comments explained that inclusion of this information could discourage women from breastfeeding even when there is no reason for concern. One comment noted that this information should only be included when there is information that breastfeeding should be withheld during drug therapy and the timing of pumping and discarding of breast milk can be provided. Alternatively, the comment suggested stating when information regarding the timing of pumping and discarding breast milk cannot be provided. Another comment noted that this information should not be obligatory when data suggest that there is not sufficient excretion of the drug in milk to cause concern for the infant. The comment explained that including this information when the "Risk Summary" and "Data" components have already stated that the drug is compatible with breastfeeding could give the false impression that the drug is unsafe for the child and may encourage women to discontinue breastfeeding. One comment noted that in cases when the drug disappears from breast milk with a known half-life, it is possible to minimize infant exposure by recommending dosing occur at certain times related to feeding.

(Response) FDA notes that information concerning minimizing exposure to the breast-fed child must be provided only to the extent it is available and relevant. In addition, the final rule was revised to clarify that information concerning minimizing drug exposure in the breast-fed

child must be included only if the drug and/or its active metabolite(s) are present in human milk in clinically relevant concentrations; the drug does not have an established safety profile in infants; and the drug is used either intermittently, in single doses, or for short courses of therapy. As discussed further in our response to Comment 84, the final rule also requires that, when applicable, the labeling describe ways to minimize a breast-fed child's oral intake of topical drugs applied to the breast or nipple skin.

(Comment 84) Topical products. In the proposed rule, FDA did not provide for inclusion of data regarding topical drugs that are not absorbed systemically by the mother but that may transfer to infants during breastfeeding. One comment requested that FDA include a standardized statement in the "Risk Summary" about such drug products.

(Response) Situations in which a topical pharmaceutical product can result in infant exposure without systemic absorption of the product into maternal serum are limited to topicals applied to the skin of the breast, especially that of the nipple and areola. For prescription drug products, these topicals would most likely include corticosteroids and anti-infectives. FDA acknowledges that the proposed rule did not accommodate a situation in which a drug product does not result in maternal systemic exposure but could result in infant systemic exposure. In response to this comment, FDA revised the "Minimizing exposure" portion of "Clinical Considerations" to accommodate the inclusion of information about such products. In the final rule, FDA added a requirement that, when applicable, the labeling must also describe ways to minimize a breast-fed child's oral intake of topical drugs applied to the breast or nipple skin.

iii. Drug effects in the breast-fed child and monitoring for adverse reactions

FDA proposed that the "Clinical Considerations" portion of the "Lactation" subsection of prescription drug labeling include information about potential drug effects in the breast-fed child

that could be useful to caregivers, including recommendations for monitoring or responding to these effects (proposed § 201.57(c)(9)(ii)(B)(2)).

(Comment 85) FDA received one comment about this portion of the proposed "Clinical Considerations." The comment suggested that FDA omit the first part of this provision-- "information about potential drug effects in the breast-fed child"--because this information duplicates the information required to appear in the "Risk Summary" under proposed § 201.57(c)(9)(ii)(A)(3), "Effects of drug on the breast-fed child." The comment also stated that the term "recommendations" in the second part of this provision could interfere with the practice of medicine. The comment suggested the following language: "Information about ways to monitor for, or respond to, potential drug effects in the breast-fed child that could be useful to caregivers."

(Response) FDA acknowledges that this portion of the proposed rule appeared to require information duplicative of information in the "Risk Summary." We removed the language, "information about potential drug effects in the breast-fed child," from the "Clinical Considerations" portion of the "Lactation" subsection of the final rule. In the final rule, when relevant information is available about potential adverse effects in an infant due to exposure to the maternal drug and/or its active metabolite(s) through human milk, this information must be included in the "Risk Summary." FDA also concluded that it was not necessary to characterize information about the potential effects of a drug and/or its active metabolite(s) on a breast-fed child as being useful to caregivers because, although caregivers sometimes read prescription drug labeling, it is not directed at them, and individual health care providers are in the best position to discuss with their patients information that may be useful for the patients to share

with other caregivers. Therefore, the reference to information that may be useful to caregivers also has been removed.

FDA acknowledges the comment concerning the use of the term "recommendations" in the second part of this provision, and in the final rule has removed the term "recommendations for monitoring" and replaced it with "available interventions for monitoring or mitigating." The final rule requires that under "Clinical Considerations" the labeling describe information about available interventions for monitoring or mitigating the adverse reactions described in the "Risk Summary." We note that this language is consistent with the language in the "Pregnancy" subsection.

iv. Dose adjustments

(Comment 86) One comment stated that dose adjustment information should not be included in the "Lactation" subsection. The comment suggested that dosing information generally should be restricted to the "Dosage and Administration" section of labeling.

(Response) FDA agrees with the suggestion that we omit information about dose adjustments from the "Lactation" subsection of prescription drug labeling, although this decision is not based on a conclusion (as suggested in the comment) that dosing information generally should be restricted to the "Dosage and Administration" section of labeling. FDA has determined that other than during the immediate postpartum period when a woman's physiology is reverting from a pregnant to a nonpregnant state, a lactating woman is unlikely to require dose adjustments for drugs. The physiological changes associated with lactation are unlikely to result in pharmacokinetic changes significant enough to warrant maternal dose adjustments. Therefore, FDA has determined that all available and relevant information about dose adjustments during pregnancy and the postpartum period must be included in the "Pregnancy" subsection of

labeling. In the final rule, FDA has removed the requirement that information about dosing adjustments during lactation be included in the "Lactation" subsection of labeling.

d. Data

FDA proposed that under the subheading 'Data,' the 'Lactation' subsection of the labeling must provide an overview of the data that are the basis for the risk summary and clinical considerations (proposed § 201.57(c)(9)(ii)(C)). FDA received comments about this portion of the rule. One comment expressed support for presenting lactation data under "Data" when available. The other comments and changes we made in response to those comments are explained in this section of the document.

(Comment 87) FDA received comments requesting that the Agency clarify when animal lactation data should be included in labeling. Several comments questioned the usefulness of animal lactation data in the absence of clinical data. One comment stated that extrapolation of animal data to humans may not be helpful without stating what is known about the correlation to humans.

Several comments stated that only human data should be presented when it is available. Two comments requested that if, in cases where both human and animal data are available, FDA decides to retain the requirement that both kinds of data be presented, the "Lactation" subsection be revised to state that clinical data are to be presented before preclinical data.

One comment requested additional clarification regarding the quantity and quality of animal data that would support inclusion of the data in labeling, and asked that FDA provide sample labeling for a drug for which only animal lactation data are available. Another comment suggested that the labeling state when there is an absence of available or sufficient human and/or animal data in the "Lactation" subsection.

(Response) The preamble to the proposed rule did not include a discussion of animal lactation data, and the inclusion of animal lactation data was not addressed in the codified section of the proposed rule. In the final rule, under "Risk Summary," FDA defines situations for which animal lactation data must and must not be included in the "Lactation" subsection. Animal lactation data can be helpful in predicting whether a drug and/or its active metabolite(s) will be present in human milk; however, because of species-specific differences in lactation physiology, animal lactation data typically do not reliably predict drug levels in human milk. FDA added a requirement to the final rule that when relevant human lactation data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans. In addition, under "Risk Summary," "Presence of drug in human milk," FDA clarified that 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. Although animal data do not reliably predict whether a drug and/or its active metabolite(s) will be present in human milk, in the absence of human data, FDA determined that the fact that a drug and/or its active metabolite(s) were or were not detected in animal milk may nevertheless be useful in informing prescribing decisions.

In the final rule, FDA revised the "Data" portion of the "Lactation" subsection to require that the labeling "describe the data that are the basis for the Risk Summary and Clinical Considerations" and removed the requirement that the labeling "provide an overview of the data." FDA made this change to clarify that under "Data," the labeling must include a more detailed description of the data than might be understood from use of the term "overview," as well as to maintain consistency between the "Data" portions of the "Lactation" and "Pregnancy" subsections. Furthermore, this subheading is only required to the extent that there are data that

are the basis for the Risk Summary and Clinical Considerations subheadings, and the headings under them.

3. 8.3 Females and Males of Reproductive Potential

In the final rule, FDA is adding a requirement that information regarding pregnancy testing, contraception, and infertility be relocated in labeling under subsection "8.3 Females and Males of Reproductive Potential." FDA is adding this requirement to the final rule based on public comments regarding these issues, and based on the Agency's conclusion that this information should be presented in labeling in a consistent location. Subsection "8.3 Females and Males of Reproductive Potential" includes three subheadings, "Pregnancy Testing," "Contraception," and "Infertility." Each subheading should only be included if it is applicable or if relevant information is available, and Section 8.3 should be omitted in its entirety if none of the subheadings are applicable. The comments are discussed in detail in our responses to Comments 88, 89, and 90.

Information concerning pregnancy testing, contraception, and infertility is important for informing decisions made by patients, in consultation with their health care providers, regarding the use of prescription drugs before or during pregnancy. This information is in many ways inherently linked to the scientific and medical rationale underpinning the Pregnancy subsection of prescription drug labeling. However, in the course of developing this final rule, and in particular in evaluating comments 88, 89, and 90, FDA concluded that because there was no consistent placement in the labeling of information about pregnancy testing, contraception, and infertility, it was difficult for health care providers to find this important information. For example, clinical advice on infertility might be found with the discussion of animal data in the "Nonclinical Toxicology" section, in the "Adverse Reactions" section, or in the "Warnings and

Precautions" section. Contraception and pregnancy testing recommendations for known or suspected teratogens might be found in the "Pregnancy" subsection or in the "Warnings and Precautions" section.

(Comment 88) FDA received one comment suggesting that the new labeling explicitly state that a woman taking drugs with potential or known adverse effects on pregnancy outcomes should (1) consider using reliable contraception if she does not intend to become pregnant or (2) if she does intend to become pregnant, seek consultation with her health care provider to discuss medical management of her health condition before becoming pregnant, if possible.

(Response) FDA agrees that when a drug has a potential or known adverse effect on pregnancy outcomes (e.g., is a known or suspected human teratogen), information regarding recommendations or requirements regarding contraception use must be included in prescription drug labeling. In the final rule, FDA requires that when contraception is required or recommended before, during, or after drug therapy, this information must be included under the subheading "Contraception" in subsection "8.3 Females and Males of Reproductive Potential." In addition, it may be appropriate to include in this subsection information concerning counseling females of reproductive potential about pregnancy planning.

Furthermore, the concerns expressed in the comment regarding the inclusion of information about contraception use when taking a drug with potential or known adverse effects on pregnancy outcomes apply equally to information about pregnancy testing, particularly when a drug is a known or suspected human teratogen. Therefore, FDA has determined that information regarding recommendations or requirements concerning pregnancy testing before, during, or after drug therapy must also be included in prescription drug labeling. In the final

rule, FDA requires that this information be included under the subheading "Pregnancy Testing" in subsection "8.3 Females and Males of Reproductive Potential."

(Comment 89) FDA received three comments noting that the "Pregnancy" subsection of the proposed rule only addresses risks to the fetus when the drug is administered to a pregnant woman, and it does not address the potential for manifestations of developmental toxicity associated with fetal drug exposure from transfer of drug through semen to the maternal and fetal circulations. One of the three comments noted that the proposed rule does not address the potential for manifestations of developmental toxicity associated with exposure resulting from transfer through the semen or the need for male contraception when a compound is determined to have a predicted risk of developmental toxicity and the transfer of semen is unknown. This comment suggested that statements addressing this issue be added when the information is required for the product. One of the comments suggested that FDA add a section to the final rule that addresses prescribing information for male patients with a partner of reproductive potential or a pregnant partner. Another comment suggested that the risk conclusion statement specify whether it is based on maternal or paternal exposure when that information is available.

(Response) FDA agrees that when relevant information is available, this information should be included in labeling. In the final rule, FDA requires that information about recommended or required use of contraception by men be included under the subheading "Contraception" in subsection "8.3 Females and Males of Reproductive Potential."

(Comment 90) FDA received one comment requesting that the Agency clarify how and when animal data described in subsection 13.1 of labeling ("Carcinogenesis, Mutagenesis, Impairment of Fertility") that raises concerns about mutagenesis, impairment of fertility, or pre-implantation loss should be included in subsection "8.1 Pregnancy." The comment also

requested that FDA clarify when it would be appropriate to move information from subsection 13.1 to subsection 8.1 or to cross-reference subsection 13.1 in subsection 8.1.

(Response) As stated previously, FDA concluded that it is important to include information about drug-associated fertility effects in labeling in a consistent location and manner. In the final rule, animal data that raise concerns about drug-associated impairment of fertility and/or pre-implantation loss effects must be included under "Infertility" in subsection "8.3. Females and Males of Reproductive Potential." In addition, when there are contraception recommendations based on animal mutagenesis data, this information must be included in subsection 8.3 under the Contraception subheading. Because the same concerns about drug-associated fertility effects apply to human data, FDA has determined that human data that raise such concerns also must be included in the "Infertility" subsection. With respect to the question about cross-referencing, subsection 8.3 should cross-reference the applicable animal data included in subsection 13.1, consistent with FDA's cross-referencing regulations (e.g., § 201.57(c)(1), (c)(6)(iv), and (c)(15)(ii)). The draft guidance on pregnancy and lactation labeling, which is being published concurrently with this final rule, addresses these issues.

IV. Implementation

FDA proposed that holders of applications (including an NDA, BLA, or efficacy supplement) approved before June 30, 2001, would be required to remove the pregnancy category from their labeling within 3 years after the effective date of this rule. These applications are those that are not subject to the requirements of the PLR. For drugs with applications (including an NDA, BLA, or efficacy supplement) approved on or after June 30, 2001, FDA proposed a phased-in implementation plan that would stagger the required dates these products would be required to replace the content and formatting of the pregnancy and lactation

subsections of their labeling with the new content and formatting required by this rule. These applications are those that are subject to the requirements of the PLR.

Table 1 contains the implementation plan that was included in the proposed rule. In table 1, "Applications" includes NDAs, BLAs, and efficacy supplements.

Table 1.--Implementation Plan	
Applications Required To Conform to New Pregnancy/Lactation Content Requirements	Time by Which Labeling with New Pregnancy/Lactation Content Must Be Submitted to FDA for Approval
<u>New or Pending Applications:</u>	
Applications submitted on or after the effective date of the pregnancy final rule	Time of submission
Applications pending on the effective date of the pregnancy final rule	4 years after the effective date of pregnancy final rule or at time of approval, whichever is later
<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 pregnancy final rule
Applications approved any time from June 30, 2007, up to and including the effective date of the pregnancy final rule	4 years after the effective date of pregnancy final rule
Applications approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of pregnancy final rule

(Comment 91) Two comments stated that the proposed implementation plan was confusing. One of these comments requested that FDA explain the rationale supporting the implementation schedule. Another comment stated the proposed phased-in approach for previously approved drugs may generate confusion. The comment explained that if drug labeling information and drug reference materials contain pregnancy information that is inconsistent between newly approved and previously approved drugs through a 3- to 5-year period, confusion may limit the understanding of the new labeling.

Comments disagreed about whether the length of the implementation schedule was reasonable. One comment stated that the long implementation timeline will delay the delivery of complete information. Another comment stated that FDA should expedite the implementation schedule for licensed drugs that are necessary to maintain the health status of the mother and

could harm the fetus if the mother is left untreated. This comment also suggested that the Agency should make supplemental information available in advance of the printed label. Another comment, however, expressed support for the proposal to give sponsors 3 years after the effective date of the rule to remove the pregnancy categories.

(Response) The Agency has taken all of these comments into consideration, and has decided to maintain the implementation schedule that was published in the proposed rule. The implementation schedule follows the timetable used for implementation of the PLR and works to balance the anticipated workload for the review of labels. The purpose of having a staggered approach is to avoid overburdening both the Agency and industry. The implementation plan for the final rule (also referred to as the Pregnancy and Lactation Labeling Rule (PLLR)) is modeled from the implementation plan for the PLR and experience acquired from that plan. The PLLR implementation timeline also depends on the PLR implementation and the extent to which applications are subject to the PLR.

(Comment 92) One comment expressed concern that under the proposed implementation schedule, the pregnancy categories will be removed from the labeling for some drugs before the new content required by the rule will be added to the labeling, and this could cause confusion among doctors and patients.

(Response) We would like to clarify that a holder of an application that is not subject to the PLR, and thus, not subject to the new content and format requirements of this final rule, must remove the pregnancy category from its labeling within 3 years after the effective date of this rule. A holder of an application that is subject to the PLR and thus, subject to the new content and format requirements of this rule, is not required to remove the pregnancy category until such time that it is required to submit revised labeling with the new content and format, even if that

occurs more than 3 years after the effective date of the final rule. FDA did not intend to suggest that application holders of previously approved applications subject to the PLR might, in some circumstances, be required to revise labeling twice as a part of implementation. Therefore, if a holder of an application is subject to the PLR, FDA does not anticipate that the pregnancy category will be removed from the labeling prior to submitting the revised labeling with the new content and format for that product under the PLLR implementation schedule. In conjunction with the publication of the final rule, the Agency is planning to launch an education campaign for all stakeholders, including health care providers and professional organizations, to ensure that they are well informed about the changes.

V. Legal Authority

A. Statutory Authority

FDA is revising its regulations on the format and content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section (under § 201.57) and the "Precautions" section (under § 201.80) of the labeling for human prescription drugs (in addition to the list of headings and subheadings under § 201.56(d)(1)).

FDA's revisions to the content and format requirements for prescription drug labeling are authorized by the FD&C Act and by the PHS Act. Section 502(a) of the FD&C Act deems a drug to be misbranded if its labeling is false or misleading "in any particular." Under section 201(n) of the FD&C Act (21 U.S.C. 321(n)), labeling is misleading if it fails to reveal facts that are material with respect to consequences that may result from the use of the drug under the conditions of use prescribed in the labeling or under customary or usual conditions of use. Section 502(f) of the FD&C Act deems a drug to be misbranded if its labeling lacks adequate directions for use and adequate warnings against use in those pathological conditions where its

use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users. Section 502(j) of the FD&C Act deems a drug to be misbranded if it is dangerous to health when used in the dosage or manner, or with the frequency or duration, prescribed, recommended, or suggested in its labeling.

In addition, the premarket approval provisions of the FD&C Act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Under section 505 of the FD&C Act, FDA will approve an NDA only if the drug is shown to be both safe and effective for use under the conditions set forth in the drug's labeling. Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act.

Under 21 CFR 314.125, FDA will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled uses and the product labeling complies with the requirements of part 201. Under § 201.100(d) of FDA's regulations, a prescription drug product must bear labeling that contains adequate information under which licensed practitioners can use the drug safely for their intended uses. This final rule amends the regulations specifying the format and content for such labeling.

Section 351 of the PHS Act (42 U.S.C. 262) provides legal authority for the Agency to regulate the labeling and shipment of biological products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (section 351(d) of the PHS Act). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)). Section

351(b) of the PHS Act prohibits false labeling of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

B. First Amendment

FDA's requirements for the content and format of the "Pregnancy" and "Lactation" subsections of labeling for prescription drug products are constitutionally permissible because they are reasonably related to the government's interest in ensuring the safe and effective use of prescription drug products and because they do not impose unjustified or unduly burdensome disclosure requirements. In the PLR, FDA explained in greater depth why that rule passes muster under the First Amendment (see 71 FR 3922 at 3964, January 24, 2006). That analysis is equally applicable to this final rule, and we hereby adopt that discussion by reference.

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Summary of Final Regulatory Impact Analysis

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts;

and equity). The Agency believes that this final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because our analysis suggests that some small prescription drug manufacturers and prescription drug repackagers and relabelers will incur costs that total more than 1 percent of their annual income in some years, the Agency finds that the final rule will have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The first regulations on the content and format of prescription drug labeling were established in 1979, including the requirement to assign drugs to one of five pregnancy categories. Over time, however, labeling became long, repetitive, and difficult to use. With the PLR in 2006, the Agency began to apply modern principles of effective communication to improve the quality of prescription drug labeling. However, the PLR left the content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section untouched. This decision gave the Agency sufficient time to meet with

experts and stakeholders to develop a regulatory framework that encourages applicants to prepare content that clearly communicates available information about prescription drug use during pregnancy and lactation, and in females and males of reproductive potential. With this final rule, the Agency specifically addresses the content and format of these subsections.

B. Summary of Costs and Benefits

The final regulatory impact analysis of the final rule (Ref. 2) is available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

Table 2 presents a summary of the annualized costs and benefits of the final rule over 10 years. With a 7 percent discount rate, annualized costs equal about \$9.5 million; with a 3 percent discount rate, annualized costs equal about \$9.2 million.

The final rule will require that applicants comply with new labeling content and format requirements for affected subsections for prescription drug and biological product labeling subject to the PLR under § 201.57(c)(9) (PLR labeling) and will require that applicants remove the pregnancy category from all prescription drug and biological product labeling subject to § 201.80(f)(6)(i) (non-PLR labeling). The "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section will be replaced by the "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" subsections. New information will be required to summarize the key information needed by health care providers treating females and males of reproductive potential. The information in these subsections will be presented in a narrative, following a standardized order and format with clear subheadings.

The primary objectives of the final rule are to improve labeling by updating the content and format of these subsections of prescription drug product labeling, and to remove the pregnancy category system. The Agency concluded that following a standardized structure is

essential for effective communication. The final rule is needed to ensure that these subsections contain the most up-to-date information available and provide prescribers with clinically relevant data that they can use in their decisionmaking processes. Consistent with the approach taken by the PLR, the Agency intends to provide applicants with clear guidance about the required content and format. Concurrent with the publication of this final rule, FDA is issuing a draft guidance for industry on "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products--Content and Format."

The level of effort needed to comply with the requirements of the final rule will depend on the type of labeling (PLR or non-PLR labeling) and the length of time the product has been marketed. Applicants and persons responsible for existing prescription drug and biological product labeling will incur one-time costs to revise existing labeling in years 3, 4, and 5. Applicants submitting new BLAs, NDAs, and certain efficacy supplements will incur one-time costs to gather and organize new content required by the final rule at the time they prepare labeling for the application or supplement. In addition, we estimate the additional annual printing costs for longer PLR labeling that will include new content.

We estimate that the total cost of the rule over 10 years will equal about \$88.7 million. The present value of the total costs will equal \$78.2 million with a 3 percent discount rate and \$66.8 million with a 7 percent discount rate. Over 10 years, the annualized present value will equal \$9.2 million with a 3 percent discount rate and \$9.5 million with a 7 percent discount rate.

Table 2.--Economic Data: Costs and Benefits Accounting Statement

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Benefits							
Annualized Monetized \$millions/year					7%		
					3%		
Annualized Quantified					7%		
					3%		
Qualitative	Improved quality of prescription drug labeling for health care providers						
Costs							
Annualized Monetized \$millions/year	\$9.5			2011	7%	10 years	
	\$9.2			2011	3%	10 years	
Annualized Quantified					7%		
					3%		
Qualitative							
Transfers							
Federal Annualized Monetized \$millions/year					7%		
					3%		
From/To	From:			To:			
Other Annualized Monetized \$millions/year					7%		
					3%		
From/To	From:			To:			
Effects							
State, Local or Tribal Government: No effect							
Small Business: The final rule will have significant impacts on some small pharmaceutical manufacturers and prescription drug repackagers and relabelers.							
Wages: No effect							
Growth: No effect							

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the total reporting and disclosure burdens. Included in the estimate is the time for reviewing

instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling

Description: The final rule amends FDA regulations concerning the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drugs. The final rule requires that labeling include, among other things, a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. The labeling also includes relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The final rule eliminates the current pregnancy categories A, B, C, D, and X. In addition, the "Labor and delivery" subsection has been eliminated because information on labor and delivery is included in the "Pregnancy" subsection. The final rule also requires that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential. The final rule is intended to create a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential.

Under § 201.57(c)(9)(i) and (c)(9)(ii), holders of approved applications are required to provide new labeling content in a new format--that is, to rewrite the pregnancy and lactation portions of each drug's labeling. Under § 201.57(c)(9)(iii), these application holders are also required to include a new subsection 8.3, "Females and Males of Reproductive Potential," which

requires that when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest drug-associated fertility effects, this subsection must contain this information. These application holders are required to submit supplements requiring prior approval by FDA before distribution of the new labeling, as required in § 314.70(b) or § 601.12(f)(1).

Under § 201.80(f)(6)(i), holders of approved applications are required to remove the pregnancy category designation (e.g., "Pregnancy Category C") from the "Pregnancy" subsection of the "Precautions" section of the labeling. These application holders must report the labeling change in their annual reports, as required in § 314.70(d) or § 601.12(f)(3).

The new content and format requirements of the final rule apply to all applications that are required to comply with the PLR, including: (1) Applications submitted on or after the effective date of the final rule; (2) applications pending on the effective date of the final rule; and (3) applications approved from June 30, 2001, to the effective date of the final rule.

The following submissions under the final rule are subject to the PRA:

- Applications submitted on or after the effective date of the final rule (§§ 314.50, 314.70(b), 601.2, 601.12(f)(1));
- Amendments to applications pending on the effective date of the final rule (§§ 314.60, 601.2, 601.12(f)(1));
- Supplements to applications approved from June 30, 2001, to the effective date of the final rule (§§ 314.70(b), 601.12(f)(1));
- Annual reports for applications approved before June 30, 2001, that contain a pregnancy category, to report removal of the pregnancy category letter in their labeling (§§ 314.70(d), 601.12(f)(3)).

The information collection requirements and burden estimates are summarized in tables 3 and 4 of this document. The burden estimates are based on data and timeframes used for section VII of this document (Summary of Final Regulatory Impact Analysis) and for the final regulatory impact analysis of the final rule (available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>). FDA estimates that approximately 4,000 applications containing labeling consistent with this rulemaking will be submitted to FDA during the 10-year period on or after the effective date of the final rule by approximately 390 applicants and repackagers and relabelers. The estimate of 4,000 applications includes labeling for approximately 800 applications submitted under section 505(b) of the FD&C Act or section 351 of the PHS Act, and 1,200 applications submitted under section 505(j) of the FD&C Act, and revised labeling from repackagers and relabelers for approximately 2,000 drug products. This estimate also includes labeling amendments submitted to FDA for applications pending on the effective date of the final rule. Based on data provided in section VII of this document and in the final regulatory impact analysis of the final rule, FDA estimates that for future approvals it will take applicants approximately 40 hours to prepare and submit labeling consistent with this rulemaking. The estimate of 40 hours applies only to the requirements of this rulemaking and does not indicate the total hours required to prepare and submit complete labeling for these applications. The information collection burden to prepare and submit labeling in accordance with §§ 201.56, 201.57, and 201.80 is approved by OMB under control numbers 0910-0572 and 0910-0001.

In addition, FDA estimates that approximately 10,150 supplements to applications approved from June 30, 2001, to the effective date of the final rule, or pending on the effective date, will be submitted to FDA during the third, fourth, and fifth years after the effective date to

update labeling in accordance with this final rule. This estimate includes approximately 1,080 NDA, BLA, and efficacy supplements, approximately 1,320 ANDA supplements, and labeling supplements from repackagers and relabelers for approximately 7,750 drug products. FDA estimates that approximately 390 application holders and repackagers and relabelers will submit these supplements, and that it will take approximately 120 hours to prepare and submit each supplement.

FDA also estimates that approximately 5,500 annual reports will be submitted to FDA during the third year after the effective date for applications approved before June 30, 2001, that contain a pregnancy category (5,500 includes annual reports for approximately 1,340 NDAs and BLAs and approximately 4,160 ANDAs containing labeling changes resulting from this rulemaking). FDA estimates that approximately 320 application holders will submit these annual reports, and that it will take approximately 40 hours for each submission.

As indicated in tables 3 and 4 of this document, we estimate that the total hours resulting from the information collection in this rulemaking will be approximately 1,598,000 hours. The costs associated with this rulemaking, including labor costs, are discussed in section VII of this document and in the final regulatory impact analysis of the final rule.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

Table 3.--Estimated Annual Reporting Burden¹

Type of Submission (21 CFR section)	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Supplements to applications approved 6/30/01 to effective date (§§ 314.70(b), 601.12(f)(1))	390	26	10,150 (Submitted 3rd, 4th, and 5th years after effective date)	120	1,218,000
Annual report submission of revised labeling for applications approved before 6/30/01 that contain a pregnancy category (§§ 314.70(d), 601.12(f)(3))	320	17	5,500 (Submitted 3rd year after effective date)	40	220,000
Total					1,438,000

¹ There are no capital costs or operating and maintenance costs associated with this information collection.

Table 4.--Estimated Annual Third-Party Disclosure Burden¹

Type of Submission (21 CFR section)	No. of Respondents	No of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
New NDAs/ANDAs/BLAs/efficacy supplements submitted on or after effective date, including amendments to applications pending on effective date (§§ 314.50, 314.60, 314.70(b), 601.2, 601.12(f)(1))	390	10	4,000 (Submitted during 10-year period after effective date)	40	160,000

¹ There are no capital costs or operating and maintenance costs associated with this information collection.

The information collection provisions of this final rule have been submitted to OMB for review, as required by section 3507(d) of the PRA. Prior to the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that this final rule does not contain policies that have

substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

X. References

In addition to the references placed on display in the Division of Dockets Management for the proposed rule under Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467), the following references are on display in the Division of Dockets Management under Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified all Web site addresses in this reference section, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. Decision Partners, LLC, "Evaluation of How Best to Communicate to Healthcare Providers about the Risks and Benefits of Prescription Drug Use for Pregnant and Nursing Women: A Mental Models Research Report," September 2009 (available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>).
2. Final Regulatory Impact Analysis for Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467) (available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm> and at <http://www.regulations.gov>).

3. U.S. Food and Drug Administration, "Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products--Content and Format," 2011.
4. Kweder, S. L., "Drugs and Biologics in Pregnancy and Breastfeeding: FDA in the 21st Century." Birth Defects Research Part A: Clinical and Molecular Teratology. 82(9):605-609, September 2008.
5. Adam, M. P., J. E. Polifka, and J. M. Friedman, "Evolving Knowledge of the Teratogenicity of Medications in Human Pregnancy." American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 157C(3):175-182, August 15, 2011.
6. Law, R., P. Bozzo, G. Koren, et al. "FDA Pregnancy Risk Categories and the CPS. Do They Help or Are They a Hindrance?" Canadian Family Physician. 56:239-241, March 2010.
7. U.S. Food and Drug Administration "Guidance for industry, Establishing Pregnancy Exposure Registries," 2002.
8. U.S. Food and Drug Administration "Guidance for Industry, Reproductive and Developmental Toxicities--Integrating Study Results to Assess Concerns," 2011.
9. Rynn, L., J. Cragan, and A. Correa, "Update on Overall Prevalence of Major Birth Defects--Atlanta, Georgia, 1978-2005." Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report. 57(01):1-5, January 11, 2008.
10. American College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy, 2011 (available at <http://www.acog.org/~media/For%20Patients/faq090.pdf?dmc=1&ts=20140130T1655496642>).

11. U.S. Food and Drug Administration, "Reviewer Guidance, Evaluating the Risks of Drug Exposure in Human Pregnancies," 2005.
12. U.S. Food and Drug Administration, "Guidance for industry, Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications," 2006.
13. U.S. Food and Drug Administration, "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," 2010.
14. Tracy, T. S., et al. "Temporal Changes in Drug Metabolism (CYP1A2, CYP2D6 and CYP3A Activity) During Pregnancy." American Journal of Obstetrics and Gynecology. 192(2):633-639, February 2005.
15. Anderson, G. D., "Pregnancy-Induced Changes in Pharmacokinetics." Clinical Pharmacokinetics. 44(10):989-1008, 2005.
16. American Academy of Pediatrics Policy Statement. "Breastfeeding and the Use of Human Milk." Pediatrics. 129(3):e827-841, 2012.
17. Sachs, H. C. and Committee on Drugs. "The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics." Pediatrics. 132(3):e796-809, September 2013.
18. U.S. Food and Drug Administration, "Draft Guidance for industry Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling," 2005.

19. Proposed Pregnancy and Lactation Labeling Rule (available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>).

20. Public Comments on Proposed Pregnancy and Lactation Labeling Rule (available at <http://www.regulations.gov/#!docketDetail;D=FDA-2006-N-0515>).

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201--LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

§ 201.56 [Amended]

2. Amend § 201.56 in paragraph (d)(1) by removing from the list of headings and subheadings the subheadings "8.2 Labor and delivery" and "8.3 Nursing mothers" and adding in their places the subheadings "8.2 Lactation" and "8.3 Females and Males of Reproductive Potential", respectively.

3. Amend § 201.57 by revising paragraphs (c)(9)(i), (ii), and (iii) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

* * * * *

(c) * * *

(9) * * *

(i) 8.1 Pregnancy. This subsection of the labeling must contain the following information in the following order under the subheadings "Pregnancy Exposure Registry," "Risk Summary," "Clinical Considerations," and "Data":

(A) Pregnancy exposure registry. If there is a scientifically acceptable pregnancy exposure registry for the drug, contact information needed to enroll in the registry or to obtain information about the registry must be provided following the statement: "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy."

(B) Risk summary. The Risk Summary must contain risk statement(s) based on data from all relevant sources (human, animal, and/or pharmacologic) that describe, for the drug, the risk of adverse developmental outcomes (i.e., structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth). When multiple data sources are available, the statements must be presented in the following order: Human, animal, pharmacologic. The source(s) of the data must be stated. The labeling must state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. If such information is available for the population(s) for which the drug is labeled, it must also be included. When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary. When applicable, risk statements as described in paragraphs (c)(9)(i)(B)(1) and (2) of this section must include a cross-reference to additional details in the relevant portion of the "Data" subheading in the "Pregnancy" subsection of the labeling. 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: "(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."

(1) 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, the Risk Summary must summarize the specific developmental outcome(s); their incidence; and the effects of dose, duration of exposure, and 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 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 the disease or condition for which the drug is indicated, the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population. The Risk Summary must state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

(2) Risk statement based on animal data. When animal data are available, the Risk Summary must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. This statement must include: The number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring. When animal studies do not meet current standards for nonclinical developmental toxicity studies, the Risk Summary must so state. When there are no animal data, the Risk Summary must so state.

(3) Risk statement based on pharmacology. When the drug has a well-understood mechanism of action that may result in adverse developmental outcome(s), the Risk Summary must explain the mechanism of action and the potential associated risks.

(C) Clinical considerations. Under the subheading "Clinical Considerations," the labeling must provide relevant information, to the extent it is available, under the headings "Disease-associated maternal and/or embryo/fetal risk," "Dose adjustments during pregnancy and the postpartum period," "Maternal adverse reactions," "Fetal/Neonatal adverse reactions," and "Labor or delivery":

(1) Disease-associated maternal and/or embryo/fetal risk. If there is a 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 to be used, the labeling must describe the risk.

(2) 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.

(3) Maternal adverse reactions. If use of the drug is associated with a maternal adverse reaction that is unique to pregnancy or if a known adverse reaction occurs with increased frequency or severity in pregnant women, the labeling must describe the adverse reaction and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction.

(4) Fetal/Neonatal adverse reactions. If it is known or anticipated that treatment of the pregnant woman increases or may increase the risk of an adverse reaction in the fetus or neonate, the labeling must describe the adverse reaction, the potential severity and reversibility of the

adverse reaction, and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk.

(5) Labor or delivery. If the drug is expected to affect labor or delivery, the labeling must provide information about the effect of the drug on the pregnant woman and the fetus or neonate; the effect of the drug on the duration of labor and delivery; any increased risk of adverse reactions, including their potential severity and reversibility; and must provide information about available intervention(s) that can mitigate these effects and/or adverse reactions. The information described under this heading is not required for drugs approved for use only during labor and delivery.

(D) Data--(1) "Data" subheading. Under the subheading "Data," the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(2) Human and animal data headings. Human and animal data must be presented separately, beneath the headings "Human Data" and "Animal Data," and human data must be presented first.

(3) Description of human data. For human data, the labeling must describe adverse developmental outcomes, adverse reactions, and other adverse effects. To the extent applicable, the labeling must describe the types of studies or reports, number of subjects and the duration of each study, exposure information, and limitations of the data. Both positive and negative study findings must be included.

(4) Description of animal data. For animal data, the labeling must describe the following: Types of studies, animal species, dose, duration and timing of exposure, study findings, presence or absence of maternal toxicity, and limitations of the data. Description of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes.

Animal doses or exposures must be described in terms of human dose or exposure equivalents and the basis for those calculations must be included.

(ii) 8.2 Lactation. This subsection of the labeling must contain the following information in the following order under the subheadings "Risk Summary," "Clinical Considerations," and "Data":

(A) Risk summary. When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the "Data" subheading in the "Lactation" subsection of the labeling. When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans. When use of a drug is contraindicated during breastfeeding, this information must be stated first in the Risk Summary.

(1) Drug not absorbed systemically. If data demonstrate that the drug is not systemically absorbed by the mother, the Risk Summary must contain only the following statement: "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)."

(2) Drug absorbed systemically. If the drug is absorbed systemically, the Risk Summary must describe the following to the extent relevant information is available:

(i) 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. If there are no data to assess this, the Risk Summary must so state. If studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the Risk Summary must state the limits of the assay used. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk, the Risk Summary must state the concentration of the drug and/or its active metabolite(s) in human

milk and the actual or estimated daily dose for an infant fed exclusively with human milk. The actual or estimated amount of the drug and/or its active metabolite(s) ingested by the infant must be compared to the labeled infant or pediatric dose, if available, or to the maternal dose. If studies demonstrate the presence of the 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 breast-fed child, the Risk Summary must describe the disposition of the drug and/or its active metabolite(s). 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.

(ii) Effects of drug on the breast-fed child. The Risk Summary must include information, on the known or predicted effects on the child from exposure to the drug and/or its active metabolite(s) through human milk or from contact with breast or nipple skin (for topical products). The Risk Summary also must include information on systemic and/or local adverse reactions. If there are no data to assess the effects of the drug and/or its active metabolite(s) on the breast-fed child, the Risk Summary must so state.

(iii) Effects of drug on milk production. The Risk Summary must describe the effects of the drug and/or its active metabolite(s) on milk production. If there are no data to assess the effects of the drug and/or its active metabolite(s) on milk production, the Risk Summary must so state.

(3) Risk and benefit statement. For drugs absorbed systemically, unless breastfeeding is contraindicated during drug therapy, the following risk and benefit statement must appear at the end of the Risk Summary: "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 breast-fed child from (name of drug) or from the underlying maternal condition."

(B) Clinical considerations. Under "Clinical Considerations," the following information must be provided to the extent it is available and relevant:

(1) Minimizing exposure. The labeling must describe ways to minimize exposure in the breast-fed child if: The drug and/or its active metabolite(s) are present in human milk in clinically relevant concentrations; the drug does not have an established safety profile in infants; and the drug is used either intermittently, in single doses, or for short courses of therapy. When applicable, the labeling must also describe ways to minimize a breast-fed child's oral intake of topical drugs applied to the breast or nipple skin.

(2) Monitoring for adverse reactions. The labeling must describe available intervention(s) for monitoring or mitigating the adverse reaction(s) presented in the Risk Summary.

(C) Data. Under the subheading "Data," the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(iii) 8.3 Females and males of reproductive potential. When pregnancy testing and/or contraception are required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects, this subsection of labeling must contain this information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility," in that order.

* * * * *

§ 201.80 [Amended]

4. Amend § 201.80 as follows:

- a. Remove the paragraph heading "Pregnancy category A." and the words "Pregnancy Category A." from paragraph (f)(6)(i)(a);
- b. Remove the paragraph heading "Pregnancy category B." and the words "Pregnancy Category B." both times they appear from paragraph (f)(6)(i)(b);
- c. Remove the paragraph heading "Pregnancy category C." and the words "Pregnancy Category C." both times they appear from paragraph (f)(6)(i)(c);
- d. Remove the paragraph heading "Pregnancy category D." and the words "Pregnancy Category D." from paragraph (f)(6)(i)(d); and
- e. Remove the paragraph heading "Pregnancy category X." and the words "Pregnancy Category X." from paragraph (f)(6)(i)(e).

Dated: November 25, 2014.

Leslie Kux,

Associate Commissioner for Policy.

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