DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. FDA–2006–N–0515] (formerly Docket No. 2006N–0467)

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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations concerning the format and content 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 agency is proposing to require that labeling include a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. The labeling would also include relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and/or lactation. The proposal would eliminate the current pregnancy categories A, B, C, D, and X. The ''Labor and delivery'' subsection would be eliminated because information on labor and delivery is included in the proposed ''Pregnancy'' subsection. The proposed rule is intended to create a consistent format for providing information about the effects of a drug on pregnancy and lactation

that will be useful for decisionmaking by women of childbearing age and their health care providers.

DATES: Submit written or electronic comments on the proposed rule by [*insert date 90 days after date of publication in the* **Federal Register**]. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by [*insert date 30 days after date of publication in the* **Federal Register**], (see the ''Paperwork Reduction Act of 1995'' section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA–2006–N–0515 and/or RIN number 0910–AF11, by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the ''Paperwork Reduction Act of 1995'' section of this document).

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you

to continue to submit electronic comments by using the Federal eRulemaking Portal, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts, and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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I. Current Pregnancy, Labor and Delivery, and Lactation Labeling

Under the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352 and 355), FDA has responsibility for ensuring that prescription drug and biological products (both referred to as ''drugs'' in this proposed 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 (21 CFR part 201) (44 FR 37434, June 26, 1979).[1] The requirements on content and format of labeling for human prescription drug and biological products were revised on January 24, 2006 (71 FR 3922).[2] As part of the 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 (21 CFR part 201) was not revised, but they were redesignated as §§ 201.57(c)(9)(i) through (c)(9)(iii). The previous labeling regulation (adopted in 1979) was redesignated § 201.80, and this regulation applies to products not affected by the January

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

[2] FDA's regulations governing the content and format of labeling for human prescription drug products are contained in §§ 201.56, 201.57, and 201.80. Although those regulations do not specifically mention the term ''biologics,'' under the act most biologics are drugs that require a prescription and, thus, are subject to these regulations.

24, 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 current regulations provide that, unless a drug is not absorbed systemically and is not known to have a potential for indirect harm to a fetus, a ''Pregnancy'' subsection must be included within the ''Use in Specific Populations'' section of the labeling. The ''Pregnancy'' subsection must contain information on the drug's teratogenic effects and other effects on reproduction and pregnancy. 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 must also be included. The regulations require 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.

Currently, §§ 201.57(c)(9)(i)(A)(1) through (c)(9)(i)(A)(5) and 201.80(f)(6)(i)(a) specify the following pregnancy category designations and language:

- *Pregnancy Category A*

For pregnancy category A, if adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state:

Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed.

If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state:

Reproduction studies have been performed in (*kinds of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*).

- *Pregnancy Category B*

For pregnancy category B, if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling must state:

Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state:

Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans

cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.

- *Pregnancy Category C*

For pregnancy category C, if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state:

Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling must state:

Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed.

- *Pregnancy Category D*

For pregnancy category D, if there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state: ''Pregnancy Category D. See 'Warnings and Precautions' section'' (for § 201.57(c)(9)(i)(A)(4)) or ''Pregnancy Category D. See 'Warnings' Section'' (for § 201.80(f)(6)(i)(d)). Under the ''Warnings and Precautions'' or ''Warnings'' section, the labeling must state:

(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

- *Pregnancy Category X*

For pregnancy category X, if studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit, the labeling must state: ''Pregnancy Category X. See 'Contraindications' section.'' Under ''Contraindications,'' the labeling must state:

(*Name of drug*) may (*can*) cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) (*Name of drug*) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

With regard to labor and delivery, the current regulations state at § 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, under current FDA regulations, a ''Nursing mothers'' subsection must be included in either the ''Use in Specific Populations'' section of the labeling (§ 201.57(c)(9)(iii)) or the ''Precautions'' section of the labeling (§ 201.80(f)(8)). The ''Nursing mothers'' subsections

provide that if a drug is absorbed systemically, the labeling must contain information about excretion of the drug in human milk and effects on the nursing infant, as well as a description of any pertinent adverse effects observed in animal offspring. The ''Nursing mothers'' subsections require the use of certain standard statements.

If the drug is known to be excreted in human milk and is associated with serious adverse reactions or has a known tumorigenic potential, the labeling must state: ''Because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.''

If the drug is known to be excreted in human milk, but is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must state: ''Caution should be exercised when (*name of drug*) is administered to a nursing woman.''

If information on excretion in human milk is unknown and the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling must state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.''

If information on excretion in human milk is unknown, but the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (*name of drug*) is administered to a nursing woman.''

II. FDA's Examination of Pregnancy Labeling

A. Part 15 Hearing on the Pregnancy Labeling Categories

In September 1997, the agency held a part 15 hearing (21 CFR part 15) on the current category requirements for pregnancy labeling (62 FR 41061, July 31, 1997). The agency sought comment on the practical utility and effects of the pregnancy categories as well as on problems associated with the categories. The agency also sought input on ways to address problems with the categories, including suggestions for possible alternatives to the categories for communicating information on reproductive and developmental toxicity. The following are the specific issues the agency sought comment and data on, followed by a summary of the comments received and the discussion related to those comments:

(1) *The agency requested comment on the extent to which the category designations are relied upon in making decisions about drug therapy in pregnant women and women of childbearing potential and decisions about inadvertent fetal exposure, the extent to which such reliance may be misplaced, and the extent to which such reliance may have untoward public health consequences.*

Participants stated that because the categories appear to provide a simple, convenient measure of risk, they are routinely relied upon by health care

providers and others in making decisions about drug therapy in pregnant women and women of childbearing age. There was concern that, because these decisions are more complex than the category designations suggest, such reliance may often be misplaced and could result in poorly informed clinical decisionmaking.

(2) *The agency requested comment on the extent to which current pregnancy labeling (category designation and accompanying narrative text) is effective in communicating risk of reproductive and developmental toxicity.*

Participants stated that the current categories are confusing and overly simplistic and, therefore, not adequate to effectively communicate risk of reproductive and developmental toxicity. A major problem identified by the participants is that the categories convey the incorrect impression that developmental risk increases from category A to B to C to D to X when, in fact, the criteria for inclusion in the categories are not based solely on increasing risk. Categories C, D, and X also consider risk weighed against benefit. Thus, drugs in categories C or D may pose risks similar to a drug in Category X based on animal or human data, but may be categorized differently based on different risk-benefit considerations.

Participants stated that the categories also create the incorrect impression that drugs within a given category have similar potential to cause developmental toxicity. In fact, because the descriptive criteria for the individual categories focus largely on whether the available data have identified a potential hazard, they permit assignment of drugs to the same category when the severity, incidence, and types of risk may be quite different. The criteria also permit drugs with known risks and drugs with no known risks to be placed in the same category. Specifically, category C (which

includes more than 60 percent of all products with a pregnancy category)[3] includes both drugs with demonstrated adverse reproductive effects in animals and drugs for which no animal studies have been performed.

Participants also expressed concern that current labeling can be confusing because the way risk is characterized does not readily discriminate among potential developmental adverse effects on the basis of severity, incidence, or type of adverse effects, nor does it make a distinction between the nature of the data (e.g., possible effects in humans based on animal data versus known effects that have been observed in humans) and the quality of the data (e.g., statistical significance, study design) that identified the effects. In addition, current labeling often does not indicate whether there are degrees of risk based on the dose, duration, frequency, route of exposure, and gestational timing of exposure to a given product.

(3) *The agency requested comment on the extent to which current pregnancy labeling may not adequately address the range of issues that may bear on decisions about drug therapy in pregnant women and women of childbearing potential and decisions about inadvertent fetal exposure (e.g., indication-specific concerns, pregnancy status, magnitude of exposure, incidental exposure, chronic exposure, timing of exposure).*

Participants stated that current pregnancy labeling does not adequately address the range of clinical situations in which information about drug exposure in pregnancy is needed. Specifically, current pregnancy labeling focuses almost entirely on prospective considerations of whether to prescribe a drug for a pregnant woman and rarely addresses inadvertent exposure. However, because approximately 50 percent of pregnancies are unplanned

[3] Based on searches of the 2001 and 2002 electronic version of the *Physicians' Desk Reference* (Ref. 39).

(Ref. 1), there is significant potential for inadvertent exposure to a drug before a pregnancy is detected. Participants expressed strong support for addressing inadvertent exposure issues in pregnancy labeling because clinical decisions about inadvertent exposures often involve deciding whether to terminate pregnancies due to the exposure. It was also pointed out that a statement about the risk associated with use of a drug during pregnancy should be put in the context of the background risk of adverse fetal outcomes.

(4) *The agency requested comment on additional information (data or interpretation of data) that could be included in pregnancy labeling to better address the range of issues that bear on decisions about drug therapy in pregnant women and women of childbearing potential and decisions about inadvertent fetal exposure*.

Participants stated that current pregnancy labeling does not adequately address the full range of potential developmental toxicities—fetal death, structural malformations, perturbations of fetal growth, and functional deficits. There were also concerns that current labeling does not present enough of the evidentiary basis for the category designation or adequately discuss the potential relevance of animal data to humans. Participants urged FDA to implement a mechanism to routinely update the ''Pregnancy'' subsection of labeling after a drug is marketed to include human exposure information as it becomes available. Several participants spoke favorably about the utility of pregnancy exposure registries. FDA was also encouraged to expand its assessment of the adequacy of pregnancy labeling to include what was then called the ''Nursing mothers'' subsection and to incorporate discussions of a product's effects on fertility, pregnancy, and lactation into a single labeling subsection. Some participants also expressed concern that current pregnancy

labeling fails to discuss the risks, sometimes serious, of foregoing medically necessary medication during pregnancy.

(5) *The agency requested comment on options to improve communication of reproductive and developmental risk in labeling, which could include alternatives to the categories (both content and format options) or efforts to make the current category scheme and accompanying narrative text more consistent and informative.*

Most participants stated that the current letter categories should be replaced with a concise narrative summarizing a product's risks to pregnant women and women of childbearing age, and the clinical implications of such risks. To aid comprehension and facilitate evaluation of therapeutic options, it was recommended that the narratives contain common core elements. Some comments also supported providing a conclusive statement or recommendation about clinical use. FDA also was encouraged to take steps to better understand how language used in pregnancy labeling to communicate risk is perceived by health care providers.

B. Development of a Model Pregnancy Labeling Format

After the part 15 hearing testimony and comments, FDA decided to revise its pregnancy labeling regulations and began to develop a model format to address the concerns raised about the existing format. The model format was designed to prominently display important information relevant to managing the risks of fetal and maternal adverse effects in the clinical setting, provide a summary of the risks that are the basis for the clinical care recommendations, and provide an overview of the data that are the basis for the risk conclusions. Accordingly, the model format divided the ''Pregnancy'' subsection into three components: (1) Clinical management statement, (2) summary risk assessment,

and (3) discussion of data. The model format replaced the letter categories with concise conclusions about risk presented in narrative form, in large part to address concerns that users of the labeling might misinterpret the categories as presenting gradations of risk and as indicating that drugs in a given category pose similar risks. The model format also separated clinical management information from the risk assessment. This separation was intended to address concerns that the current categories (category X, in particular) appear to represent only risk assessments, but, in some cases, actually represent risk-benefit considerations. The three distinct labeling components were intended to clearly differentiate between the clinical management information, the risk conclusions, and the data that underpin the risk conclusions.

C. Focus Group Testing of Model Pregnancy Labeling Format

FDA sought practical feedback on the model format the agency had developed for the ''Pregnancy'' subsection at the 15th Annual Clinical Update in Obstetrics and Gynecology Conference in February 1999 (February 1999 Conference). At this conference, FDA conducted two focus groups that included obstetrician-gynecologists and family practitioners. One of the groups also included a reproductive endocrinologist.

Participants were provided with sample ''Pregnancy'' subsections of labeling for three fictitious drugs. One sample used the current pregnancy labeling format and the other two used the model format that FDA had developed based on recommendations from the part 15 hearing. The feedback the agency sought and the responses it received from the participants were as follows:

(1) *What factors did they take into account when prescribing for a pregnant woman and what information did they rely on?*

Focus group members indicated that they rely on the pregnancy categories as a guide for prescribing and that they also rely on colleagues for advice.

(2) *What was the availability and quality of data they relied on in making prescribing decisions for pregnant women?*

The major concern of focus group members was the absence of human data. They indicated a willingness to rely on animal data in the absence of human data if the labeling provided some correlation to human dosing. They also recommended that if human data were available, they should take precedence over animal data in making risk conclusions.

(3) *What were their overall impressions of the sample labeling formats, including their thoughts about the formats generally and the clinical management section in particular?*

Focus group members preferred the model pregnancy labeling formats that had been developed based on recommendations from the part 15 hearing. They agreed that the clinical recommendations should appear first in the labeling, followed by the details. They favored a clinical management section, but there was some difference of opinion as to how directive the management advice should be. While some members said they appreciated the directive nature of the new labeling formats, other participants were uncomfortable with the directive management advice. The overall consensus was that the participants wanted as much information as possible without specific instructions pertaining to clinical management.

(4) *What were their recommendations for what should be in labeling and how it should be presented?*

Focus group members recommended that animal data be arranged by species and that the data be organized by effect in trimester of pregnancy. They

also preferred a uniform labeling format for all drug products. Finally, participants stated that more information was better and that the most important information should be presented first. Specifically, they encouraged FDA to include relevant information about human exposures even if such information was limited (e.g., from a very limited number of case reports of exposures).

D. Advisory Committee Assessment of Pregnancy Labeling Concepts

Based on the part 15 hearing and the feedback from the focus groups at the February 1999 Conference, the agency further developed the model pregnancy labeling format and presented the revised version for discussion and comment at a meeting of the Pregnancy Labeling Subcommittee of the FDA Reproductive Health Drugs Advisory Committee in June 1999 (64 FR 23340, April 30, 1999). The model labeling format was presented as a Concept Paper on Pregnancy Labeling (*http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3516r1.doc*).

The agency asked the advisory committee for input on the following issues:

(1) *The committee was asked to provide comment on the usefulness of the proposed reorganization of information on pregnancy, fertility, and lactation in the labeling that separates information into three components: Clinical management, summary risk assessment, and discussion of data, including their suggestions to refine or improve the model.*

In general, committee members thought the proposed model with its standardized format was an improvement over the current labeling and that separating information into three components (clinical management statement, risk summary, and discussion of data) under the fertility, pregnancy, and

lactation subsections would be beneficial. However, they felt that the summary risk information was the most important information in the pregnancy subsection; therefore, the risk statement should precede the clinical management information. One advisory committee member recommended against including fertility, saying that fertility is a very different issue and should be considered separately.

(2) *How specific and detailed should the recommendations be in the clinical management statements (e.g., should they address types and frequency of testing and monitoring)? Were there circumstances under which specific recommendations should not be provided?*

Committee members agreed that it was important to have information relevant to clinical management of pregnant women in the labeling. However, they advised against providing directive advice or instructions (e.g., specific instructions about the type of monitoring that should be done and when to do it). They were concerned that directive advice could intrude on the practice of medicine and, if not kept current, could become outdated and contrary to the standard of care. They were also concerned about the liability implications for prescribers of failing to adhere to instructions in labeling that are no longer the standard of care for the relevant clinical situation.

Committee members also objected to the heading ‘‘Clinical Management Statement’’ because it suggested that the information is intended to dictate to health care providers how to manage their patients. They recommended that the heading be changed to ‘‘Clinical Considerations’’ to clarify that the information is intended to assist health care providers and patients in making their own decisions.

(3) *In the risk summary, how could appropriate context for the reader be provided, such as risks to pregnancy associated with the maternal disease state or baseline population rates of the adverse outcomes in question?*

Committee members agreed that the risk summary should be expressed in terms of an increased risk due to drug exposure compared to a background risk—either a background risk for a disease state or general background risk for the occurrence of the hazard in pregnancy. Some members advocated including a general statement in this section to remind readers of the inherent risks of developmental adverse effects independent of drug therapy. The committee also recommended that standardized risk statements be used and that the risk statement indicate gestational periods of higher and lower fetal vulnerability if that information is available. They felt that any description of risk should be portrayed as either ''potential'' or ''known'' depending on whether the information is based on animal studies or human experience.

(4) *Could the committee provide guidance on the relative merits of quantitative (e.g., risk ratios) vs. qualitative (e.g., high/low) descriptions of risk for this section of the label?*

There was general agreement among the committee members that quantitative description of risks is more informative and less problematic than qualitative description. Some members also expressed the view that stating the absolute or attributable risk is preferable to stating a risk ratio. Others stated they would like to see confidence intervals around numbers used because they convey information on the quantity of data.

(5) *What should the goals be for the discussion of data component? How should information be selected for inclusion?*

Committee members stated that the discussion of data component should include human data to the extent available. There was some discussion about the utility of animal data in the absence of human data. However, there was consensus among committee members that the labeling should address the relevance of animal data for the doses generally prescribed for humans.

In the model format provided to the committee members, the discussion of data component included six subheadings: Structural alteration (or dysmorphogenesis), embryo-fetal death, growth retardation (irreversible and reversible), functional toxicities, maternal toxicity, and labor and delivery. The agency's purpose in proposing these subheadings was to address the full range of possible reproductive and developmental toxicities that might be appropriate for discussion in the data component. The committee's discussion focused on animal data because most of the data in current labeling is animal data. Committee members thought that the subheadings were too detailed. Instead, it was suggested that the presentation of animal studies should focus on describing the toxicities and include dose response information. Committee members also thought it was important, with regard to animal data, to compare the level of systemic exposure in animals to the human level.

(6) *In the setting where little is known about risk, how should this lack of information be communicated in a manner that is optimally informative?*

Committee members agreed that situations where there are ''no data'' should be distinguished from those where there are ''limited data.'' They agreed that the labeling should clearly state when there are no data available. When there are some data available, but the data are not sufficient to draw a conclusion about the risk of developmental abnormality, it was suggested that the labeling should qualify the risk by saying that the risk is

undetermined. Committee members also cautioned against making the assumption that all drugs within a pharmaceutical class are teratogenic just because one member of the class is.

(7) *How could uncertainty associated with the predictive value of animal studies, particularly in the absence of human data, best be communicated?*

Some committee members stated that the uncertainty of predicting human risk based on animal data should be clearly expressed in the labeling. Other committee members suggested that in the absence of human data, instead of focusing on the uncertainty of the predictive value of the available animal data, the labeling should focus on the weight of evidence provided by the animal data.

(8) *Is there risk or other descriptive language that has acquired sufficient unintended connotation that it should be avoided in providing advice or in summary risk statements? Were there examples and could they suggest alternatives?*

There was general agreement among committee members that labeling should describe the facts. Committee members cautioned against the use of phrases or terms such as ''use with caution,'' ''crosses the placental barrier,'' and ''probability'' because the lay public and scientists define the terms very differently. One member also pointed out that all of the terms used to describe animal findings can be alarming to patients and providers.

E. Focus Group Testing of Pregnancy Risk Statements

Based on the recommendations of the advisory committee, the agency further refined the model pregnancy labeling format. FDA also developed a number of standard statements to use in pregnancy labeling to characterize the risk of developmental abnormality associated with a drug. In May 2000, FDA conducted four focus groups to evaluate these standard statements being

considered by the agency. Two focus groups consisted of nurse-midwives attending the annual meeting of the American College of Nurse-Midwives and two focus groups consisted of obstetrician/gynecologists attending the annual meeting of the American College of Obstetricians and Gynecologists (ACOG).

Participants in all four focus groups were asked to review the following series of risk statements:

Risk Statement 1

Drug X does not appear to increase the risk of (type of developmental toxicity). Data on a limited number of exposed pregnancies indicate no adverse effects on the health of the (fetus/newborn child). While animal studies did show (specific adverse effect seen in animals), such effects in humans are unlikely.

Risk Statement 2

Drug X is not expected to increase the risk of (type of developmental toxicity) attributable to Drug X. Data on a large number of exposed pregnancies indicate no adverse effects on the health of the (fetus/newborn child). Animal studies show (specific adverse effect seen in animals) but the implications for humans are uncertain.

Risk Statement 3

Drug X does not appear to increase the risk of (type of developmental toxicity). Data on a limited number of exposed pregnancies indicate no adverse effects on the health of the (fetus/newborn child). Animal studies show (specific adverse effect seen in animals) but the implications for humans are uncertain.

Risk Statement 4

Drug X may increase the risk of (type of developmental toxicity or adverse effect) based on animal studies and data on a limited number of exposed pregnancies.

Risk Statement 5

Drug X does not appear to increase the risk of (type of developmental toxicity). Data on a large number of exposed pregnancies indicate no adverse effect on the health of the (fetus/newborn child), although animal studies did show (specific adverse effect seen in animals).

Risk Statement 6

Drug X may increase the risk of (type of developmental toxicity). Data on a limited number of exposed pregnancies indicate no adverse effects on the health of the (fetus/newborn child). However, animal studies did show (specific adverse effect seen in animals).

The focus groups were asked to consider a number of phrases for possible use in risk statements, including phrases used in the six model risk statements above. These phrases included ''does not appear to increase the risk,'' ''there is no known risk attributable to,'' ''is not expected to increase the risk,'' ''may not increase the risk,'' and ''may increase the risk.'' In general, the participants did not like the use of terms such as ''may increase,'' ''may not increase,'' ''is uncertain,'' ''although,'' or ''however,'' saying they felt the words were too vague and not useful to them. They preferred a factual statement that would allow them to make a clinical judgment based on the circumstances of their patient. Participants also believed that the degree of risk that certain statements attempted to convey overlapped with that conveyed by other statements.

The physicians participating in the focus groups at the ACOG meeting also were asked to review a general statement about the risks inherent in pregnancy

independent of drug therapy, the difficulty in determining whether a drug poses any additional risk of developmental abnormality above the background incidence, and the uncertain predictive value of animal studies. The physicians agreed that it would be useful to include the general statement in labeling and said it would be particularly useful when explaining the concept of background risk to their patients.

Based on feedback from the four focus groups, FDA revised the standard risk statements in the model format and incorporated the general statement reviewed by the physician groups.

III. FDA's Examination of Labeling on Lactation

A. Recommendations on Lactation Labeling From Part 15 Hearing

Participants in the September 1997 part 15 hearing on pregnancy labeling also recommended that the agency revise the requirements for the ''Nursing mothers'' subsection of the labeling. They were concerned that current labeling on lactation is not informative for a number of reasons, including lack of data and a tendency for clinicians to conclude, based on the current format of the labeling, that they should recommend to their patients that they choose between breast-feeding and taking a drug. Based in part on these concerns, FDA developed a new format for the lactation subsection of labeling, using the draft pregnancy labeling model as a guide.

B. Advisory Committee on Lactation Labeling Issues

In September 2000, the agency held a joint advisory committee meeting of the Pregnancy Labeling Subcommittee of the Advisory Committee for Reproductive Health Drugs and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee to consider lactation labeling (65 FR 50995, August 22, 2000) (advisory committee on lactation). Committee

members heard presentations on what was then called the ''Nursing mothers'' subsection of the labeling, the need for research and information on drug therapy during lactation, and the draft format developed by FDA for the lactation portion of the labeling.

The committee members were specifically asked to address the following questions:

(1) *Is maternal drug therapy during lactation an important health issue for infants? If yes, how should fundamental data be derived to determine if a drug is expressed in breast milk; whether a drug found in breast milk is available to the infant; and, when the drug is available, what the risk or lack of risk is to the nursing infant?*

The advisory committee members agreed that maternal drug therapy during lactation is an important health issue for infants. They believed that the only type of studies that could be ethically conducted involving nursing infants would be those in which the mother had already independently made the decision to breast-feed during drug therapy. The committee agreed that serum levels in the child would provide valuable information and that it is most important to assess clinical effects on the child from drug exposure. Committee members indicated that, as a practical matter, only short-term effects could be detected. They recommended that, if there is a known pediatric dose and safety profile, the dose received via breast milk should be put in perspective by reference to the recommended pediatric dose.

(2) *What products or types of therapies are most important to study: Those for conditions common in young women; those for chronic conditions; those for life-threatening conditions? Are there characteristics that are common across products or groups of products that make them a high priority?*

After lengthy discussion of the various issues and classes of drugs, the committee recommended that studies in the following categories of drugs should be of higher priority: Drugs predicted to have high levels in breast milk; drugs commonly used by women of childbearing age; and drugs used to treat chronic illnesses.

(3) *What kinds of information should be included in the labeling to allow informed decisions as to the safety of breast-feeding while taking a medication?*

The advisory committee members recommended that labeling include the following information:

- The amount of drug in breast milk,
- The anticipated daily dose for a nursing infant,
- The effect of the drug on the infant taking into account the infant's age,
- Drug pharmacokinetics during lactation,
- The presence of metabolites in breast milk and their half-lives,
- The effect of the drug on displacement of bilirubin from protein-binding, and
- The effect of the drug on the quantity and quality of breast milk produced.

Committee members recommended against a general statement that a drug enters the breast milk without information on the quantity of drug in breast milk. The committee advised that labeling discussions about the need to discontinue breast-feeding should be put in the context of a particular drug, its importance to the mother, and any risk to the infant. One member questioned the value of including animal data in lactation labeling, saying the data can be confusing and not necessarily helpful. Committee members urged FDA to provide a mechanism to ensure that labeling is updated as new data become available.

C. The Need for Informative Lactation Labeling

Breast milk is the most complete form of nutrition for infants and offers a range of health benefits for breast-feeding women and infants. Research in developed and developing countries provides strong evidence that breast-feeding decreases the incidence and/or severity of a wide range of infectious diseases including bacterial meningitis, bacteremia, diarrhea, respiratory tract infection, necrotizing enterocolitis, otitis media, urinary tract infection, and late-onset sepsis in preterm infants. Studies suggest that breast-feeding significantly reduces postneonatal infant mortality and rates of sudden infant death syndrome in the first year of life. In addition, data suggest that older children who were breast-fed have slightly enhanced cognitive performance and decreased rates of asthma, obesity and overweight, diabetes mellitus (insulin and non-insulin dependent), lymphoma, leukemia, and Hodgkin's disease. Maternal benefits of breast-feeding include reduction in postpartum bleeding, earlier return to pre-pregnancy weight, reduced risk of premenopausal breast cancer, and reduced risk of osteoporosis (Ref. 2).

A survey conducted in 2001 found that 69.5 percent of women initiated breast-feeding and 32.5 percent had continued to breast-feed when surveyed at 6 months postpartum (Ref. 3). Given these numbers, FDA believes that it is highly likely that a woman will need and take medications while she is breast-feeding and thereby potentially will expose her child to the effects of these medications. Surveys in various countries indicate that 90 to 99 percent of nursing mothers receive a medication during the first week postpartum. At 4 months postpartum, the percentage of nursing mothers taking medication was 17 to 25 percent. Five percent of nursing mothers receive long-term drug therapy (Ref. 4).

Because lactation studies, including studies of the transfer of drug into milk (animal or human), are not usually conducted during drug development, for most drugs there is little scientific information available on the effects on milk production, the extent of passage into breast milk, and the effects on the infant. Therefore, breast-feeding women and their health care providers must make decisions about treatment of maternal medical conditions in the absence of data. FDA is aware that a decision often is made to stop breast-feeding in order to take needed drug therapy.

FDA encourages sponsors to conduct lactation studies so that women and their health care providers will have the information they need to make decisions about breast-feeding during maternal drug use. On February 8, 2005, the agency issued a draft guidance for industry entitled ''Clinical Lactation Studies—Study Design, Data Analysis, and Recommendations for Labeling'' (70 FR 6697). The draft guidance provides advice and recommendations on the design, conduct, and analysis of clinical lactation studies, including advice about when to perform such studies. It sets out in detail the types of information on lactation that the agency believes should be available to breast-feeding women and their health care providers. In addition to the public comments received on the draft guidance, the agency requested input from the Pediatric Advisory Committee at its November 29, 2007, meeting. FDA is currently working to finalize its guidance on Clinical Lactation Studies.

IV. Description of the Proposed Rule

A. General Description of the Format and Content of the Pregnancy and Lactation Subsections of Labeling

The agency is proposing to revise the format and content of § 201.57 to change the requirements for the current ''Pregnancy,'' ''Labor and delivery,''

and ''Nursing mothers'' subsections. The proposed rule would merge the current ''Pregnancy'' and ''Labor and delivery'' subsections into a single ''Pregnancy'' subsection and would modify the requirements for the format and content of that subsection. The proposed rule would modify the format and content of the ''Nursing mothers'' subsection. The agency is proposing to rename the subsection ''Lactation'' because the focus of the subsection is primarily on the breast-fed child rather than on the lactating woman. In labeling, the identifying numbers for the subsections under the section ''8 Use in Specific Populations'' would be 8.1 for ''Pregnancy'' and 8.2 for ''Lactation.'' The identifying number 8.3 would be available for future use.

B. Pregnancy Subsection

The proposed rule would amend § 201.57(c)(9)(i) by entirely replacing the format and content of the ''Pregnancy'' subsection. As discussed in section II.A of this document, the pregnancy category system has been criticized as being confusing and overly simplistic. The standardized statements required by current regulations do not distinguish information about risk alone from judgments based on both risk and benefit. In addition, the statements associated with the pregnancy categories do not take into account that a woman may already have been exposed to a drug before learning she is pregnant, and thus considerations for her may differ from those for a women who has not yet been exposed to a drug during pregnancy. The agency believes that advice and cautions about drug use should be clear and should specifically relate to the particular clinical situation, which includes whether exposure has already occurred or is being contemplated. The clinical situation also includes the risks presented if the woman has a condition or disease that remains untreated during her pregnancy.

FDA's process for developing this model for the pregnancy and lactation subsections of labeling included establishing an internal working group to obtain extensive input from experts from multiple disciplines across the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. The working group carefully explored a multitude of models to determine whether a different pregnancy category system could accurately and consistently communicate differences in degrees of maternal and fetal risk. The working group considered systems employed by other countries, including the European Union and Australia, but concluded that these approaches either did not address degrees of risk, or that these approaches simply provided statements that directed clinicians whether or not to use a product without describing risk information in a clinically meaningful way. The working group also explored developing a new model using alpha-numeric symbols or character/graphics to represent a continuum of risk. This approach included building tables and matrices of evidence-based criteria that might underlie each category along the risk continuum. When the working group 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.

FDA concluded that using a category system to characterize the risks of drug use during pregnancy would not be appropriate because of the complexity of medical decisionmaking about drug use during pregnancy. Various combinations of reproductive toxicology data, human pregnancy exposure data, and information about the mother's condition define a risk/benefit equation for each individual patient and her circumstances. As for any drug in any patient, prescribing and drug use decisions that affect both mother and

fetus require consideration of various clinical and individual factors including the effects of the drug on the mother, the severity of the mother's condition, maternal tolerance of the drug, coexisting maternal conditions, the impact of maternal illness on the fetus, and the available alternative therapies. These conclusions mirror and support feedback FDA obtained from the public through the 1997 part 15 hearing and in Advisory Committee meetings and focus groups with experts and other clinicians who care for pregnant women. The feedback from the participants in these activities made it clear that the explanation of what is meant by any determination of ''risk'' or ''hazard'' is equally, if not more, important than the risk determination itself. 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 much more complex constructs in clinical medicine than in other areas, such as environmental exposure or consumer product ratings. For similar reasons, FDA does not apply symbol or letter designations of risk to other potential toxicities or adverse effects expected with medical product use. Accordingly, FDA believes 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.

One of FDA's primary objectives in developing the model labeling format in response to the part 15 hearing and early focus group testing was to make a clear distinction between risk information and clinical management information. The model format originally contained three components in the following order: Clinical management, summary risk assessment, and discussion of data. Committee members at the June 1999 advisory committee

stated that the summary risk assessment was the most important information in pregnancy labeling and therefore should precede the clinical considerations component. FDA agrees that the risks should be presented first, followed by clinical considerations. Accordingly, under the proposed rule, pregnancy labeling would contain a fetal risk summary, clinical considerations, and data discussion, in that order. Since developing the model format, the agency has concluded that pregnancy labeling should contain two additional components: Pregnancy exposure registry information (if applicable) and a general statement about the background risk of fetal developmental abnormalities. These two components, as well as the reasons for including them, are discussed in detail below. Thus, the proposed ''Pregnancy'' subsection would require prescription drug labeling to contain, under the subheading ''8.1 Pregnancy,'' the following information: (1) Pregnancy exposure registry information (if applicable), (2) a general statement about the background risk of fetal developmental abnormalities, (3) a fetal risk summary, (4) clinical considerations, and (5) data. Information on labor and delivery would be included under clinical considerations of the pregnancy subsection because, from a medical perspective, labor and delivery is the end phase of pregnancy. FDA seeks comment on how these elements should be ordered to optimize the clinical usefulness of this labeling subsection. Specifically, FDA is interested in comments on whether the fetal risk summary should precede the pregnancy registry contact information and the information on background risk.

FDA's current regulations permit omission of the ''Pregnancy'' subsection of labeling if the drug is not absorbed systemically and is not known to have a potential for indirect harm to the fetus. In contrast, the proposed rule would require that the labeling for all drugs contain a ''Pregnancy'' subsection. The

agency believes that labeling that omits the ''Pregnancy'' subsection is confusing because the reader has no way of knowing why that subsection has been omitted. It is unlikely that most health care providers are aware that the ''Pregnancy'' subsection may be omitted when the drug is not absorbed systemically. Thus, the lack of a ''Pregnancy'' subsection does not necessarily signal to the reader that the drug is not absorbed systemically. Furthermore, in some cases, particularly with older labeling, there may be no ''Pregnancy'' subsection even when the drug is systemically absorbed. To correct this potential source of confusion, the proposed rule would require that the labeling of all drugs contain a ''Pregnancy'' subsection. However, when the drug is not systemically absorbed, the fetal risk summary would 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.''

1. Pregnancy Exposure Registry Information (Proposed § 201.57(c)(9)(i)(A))

FDA believes that appropriately conducted pregnancy exposure registries are an important mechanism for the collection of clinically relevant data concerning the effects of exposure to drugs during human pregnancy. Because of its belief in the value of pregnancy exposure registries, the agency has taken a number of steps to facilitate the establishment of well-designed pregnancy exposure registries and to encourage participation in such registries. In August 2002, the agency published a guidance for industry on ''Establishing Pregnancy Exposure Registries'' to provide sponsors with recommendations on the design of pregnancy exposure registries (67 FR 59528, September 23, 2002). FDA's Office of Women's Health maintains a Web site (*http://www.fda.gov/womens/*

registries/default.htm) that explains what a pregnancy registry is and lists pregnancy registries currently enrolling pregnant women with specific medical conditions and women using specific drugs. Providing information about pregnancy exposure registries in prescription drug labeling is an additional step to encourage participation in registries.

Data from pregnancy registries have been used to support important labeling changes for certain drugs. The agency anticipates that, under the proposed labeling format, data from pregnancy registries, among other types of data, would be used to update labeling that, in most cases, would otherwise contain only animal data, and thus labeling would provide more clinically useful information for health care providers and their patients.

The proposed rule states that, 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 stated at the beginning of the ''Pregnancy'' subsection of labeling. FDA believes that placing this information in a position of prominence in prescription drug labeling may encourage participation in pregnancy registries by making it easier for health care providers and their patients to learn of pregnancy registries and the means to contact them. This information may also be appropriate for inclusion in a Medication Guide (patient labeling) under 21 CFR part 208.

If there is no pregnancy registry for the drug, the labeling is not required to contain any statement about pregnancy registries.

2. General Statement About Background Risk (Proposed § 201.57(c)(9)(i)(B))

In all pregnancies, there is a risk that there will be an adverse outcome, even if the mother takes no medications during her pregnancy. This risk is usually referred to as the background risk. Rates of adverse pregnancy

outcomes vary with maternal age and underlying maternal medical conditions (Ref. 5). Fifteen to twenty percent of recognized pregnancies result in spontaneous abortion or miscarriage (loss prior to 20 weeks) (Ref. 6), and 1 in 200 known pregnancies results in fetal death or stillbirth (loss after 20 weeks) (Ref. 7). One out of 28 infants is born with serious birth defects (i.e., those resulting in physical or mental disability or death) (Ref. 1). Except for genetic syndromes and chromosomal abnormalities, most birth defects have no known cause. Minor birth defects may be 10 to 20 times more common than major ones, and 20 percent of infants with one or more minor birth defects also have a major birth defect (Ref. 8).

Because many women of reproductive age are not aware that there is a background risk in all pregnancies, physicians on the advisory committee and those who participated in focus testing of the model format suggested that FDA include in pregnancy labeling a general statement about background risk. The physicians stated that including such a statement would help them when counseling their patients.

FDA agrees that it is important to make clear that, when labeling characterizes the risk presented by a drug used during pregnancy, it is the increase over the background risk that is being characterized. To emphasize this point, proposed § 201.57(c)(9)(i)(B) would require pregnancy labeling to state that all pregnancies have a background risk of birth defect, loss, or other adverse outcome, regardless of drug exposure, and that the fetal risk summary describes the drug's potential to increase the risk of developmental abnormalities above the background risk.

3. Fetal Risk Summary (Proposed § 201.57(c)(9)(i)(C))

The proposed rule states that, under the subheading ''Fetal Risk Summary,'' the labeling must contain 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. The fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities and other risks (e.g., transplacental carcinogenesis) in humans.

a. *Types of developmental abnormalities and other risks*. Reproductive toxicologists refer to birth defects as developmental toxicities, and divide such toxicities into four types: (1) Dysmorphogenesis, (2) developmental mortality, (3) functional toxicity, and (4) alterations to growth (Ref. 9). Because some of this terminology is technical and unfamiliar to most health care providers, FDA is proposing to use simpler terms so that pregnancy labeling based on this proposed rule would be more easily understandable. Accordingly, FDA uses the following terms in this proposed rule:

- To describe developmental toxicities, the proposed rule uses ''developmental abnormalities.''
- To describe dysmorphogenesis, the proposed rule uses ''structural anomalies,'' which includes malformations, deformations, and disruptions.
- To describe developmental mortality, the proposed rule uses ''fetal and infant mortality,'' which includes miscarriage, stillbirth, and neonatal death.
- To describe functional toxicity, the proposed rule uses ''impaired physiologic function,'' which includes such outcomes as deafness, endocrinopathy, neurodevelopmental effects, and impairment of reproductive function.

- The proposed rule retains the term ‘‘alterations to growth,’’ which includes such outcomes as growth retardation, excessive growth, and early maturation because this term is not as technical as the others, and other terms do not adequately capture this range of outcomes.

In addition to the four types of developmental abnormalities, there may be other risks that are appropriate for discussion in the fetal risk summary, such as transplacental carcinogenesis.

FDA believes that it is important for pregnancy labeling to describe, to the extent possible, all recognized potential adverse outcomes to the fetus associated with drug use during pregnancy. This point was also made by participants at the part 15 hearing. Thus, the proposed rule provides that the fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities (i.e., structural anomalies, fetal and infant mortality, impaired physiologic function, alterations to growth) or other risks (e.g., transplacental carcinogenesis) in humans.

b. *Conclusions about risk*. The June 1999 advisory committee recommended that pregnancy labeling use standardized risk statements. Some participants at the part 15 hearing recommended that pregnancy labeling provide a conclusion statement as well as a narrative summary. Based on this feedback and its own internal deliberations, FDA believes that, to be most useful to health care providers, pregnancy labeling should draw conclusions about the likelihood that drug use during pregnancy increases the risk of developmental abnormalities, as well as describe the nature of the risk(s). Thus, the proposed rule would require that the fetal risk summary component of pregnancy labeling include language characterizing the likelihood that the drug increases the risk of developmental abnormalities or other risks in

humans by using certain standardized risk conclusions that are provided in the proposed rule. More than one risk conclusion may be needed to characterize the likelihood of risk for different developmental abnormalities, doses, durations of exposure, or gestational ages at exposure. Examples of risk conclusions for varying types of data are provided in the sample fetal risk summaries in the appendix of this document.

c. *Data sources*. In developing the fetal risk summary, 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 or other relevant risks must be considered. Participants in the part 15 hearing expressed concern that current pregnancy labeling does not clearly identify whether descriptions of, and conclusions about, risk are based on animal or human data. FDA agrees that it is critical to know the source of the information and conclusions in the fetal risk summary. Thus, the proposed rule would require that the source(s) of the data that are the basis for the fetal risk summary be stated. For example, the risk summary must state that it is based on human data or based on animal data. The proposed rule also states that the fetal risk summary must present human data before animal data.

For the fetal risk summary, the agency is proposing different approaches for communicating the risks of drug use during pregnancy depending on whether the risk is based on human data or on animal data. Although FDA is proposing the use of standardized risk conclusions both for risks based on human data and those based on animal data, the risk conclusions based on human data would be followed by a narrative discussion of the risk. The agency believes that a narrative description of human data is the best approach

for summarizing such data in a comprehensive manner because the types of human data contributing to the assessment are variable and complex. The assessment must also contribute constructively to the clinical decision to be made by the health care provider by helping her understand how the human data may or may not apply to the individual patient. In deciding whether to prescribe a drug during pregnancy, the clinician needs to consider the human data in combination with the maternal and fetal effects of not treating the maternal condition, other coexisting maternal conditions and/or medications, and whether exposure has already occurred. On the other hand, while the degree to which teratogenesis in animals predicts teratogenesis in humans varies, collective knowledge about the animal species used for reproductive toxicology studies and certain principles of reproductive toxicology provide a basis for more algorithmically characterizing expected risk in the context of animal data. It is important to emphasize that animal data can only predict that a risk exists. For this reason, and because most clinicians are not experts in reproductive toxicology, the proposed rule uses only standardized risk statements to convey risk based on animal findings, and does not include a narrative summary of the animal findings.

d. *Sources of human data*. Except for the few products developed to treat conditions unique to pregnancy, prescription drugs are not tested in pregnant women prior to their approval. Therefore, human data concerning a drug's effect(s) on pregnant women and their offspring almost never come from controlled clinical trials. When human data are available, they may come from a variety of other sources. Sources that may contribute to an evaluation of whether a drug increases the risk of developmental abnormalities include pregnancy exposure registries, cohort studies, case-control studies, case series,

and case reports. An assessment of the quality and quantity of the available human data is critical in determining the probative value of that data.

e. *The importance of human data*. FDA expects that revising our regulations on the content and format of pregnancy labeling will result in pregnancy labeling that includes much more information based on human data than does existing labeling. The importance of including human data in labeling was stressed by physicians who participated in focus group testing of the model format and also by the June 1999 advisory committee.

Participants at the part 15 hearing also emphasized that pregnancy labeling should be updated routinely to include human exposure information as it becomes available. The same principle was addressed by the Teratology Society in its comments on FDA's draft guidance for reviewers on ''Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities,'' issued in October 2001 (66 FR 56830, November 13, 2001):

> We recommend that assessment of the developmental and reproductive toxicity of every drug be seen as an ongoing process, not one that ends when the drug receives initial FDA approval. The process should encourage collection of human reproductive and developmental toxicity data after the drug has been approved and include provision for regular re-evaluation of all available data, and especially of relevant human data, as they become available.

Most health care providers are not able to translate animal reproductive toxicity data into an accurate assessment of human teratogenic risk. Thus, in the absence of human data, it is difficult for health care providers to adequately counsel patients about the risks of drug use in pregnancy. Without adequate counseling, women may decide to take steps to avoid becoming pregnant while

on needed drug therapy, to forego needed drug therapy while pregnant, or to terminate pregnancies.

Providing the most complete assessment of risk possible, including both human and animal data, is essential because complete avoidance of drug use by pregnant women is neither realistic nor beneficial to the overall wellbeing of mother and fetus. Women of reproductive age commonly use prescription drugs. A recent survey reported that 46 percent of women 18 to 44 years old had used at least one prescription drug during the preceding week, while 3 percent had used five or more (Ref. 10). Approximately 10 percent of women between the ages of 15 and 44 become pregnant annually (Ref. 11), and about half of these pregnancies are unplanned (Ref. 1). Thus, it is not uncommon for a fetus to be exposed to drugs before a woman knows she is pregnant. In many cases, such exposure would likely occur during the critical period of organogenesis (3 to 8 weeks postconception) (Ref. 12).

Some women enter pregnancy with medical conditions that require ongoing or episodic treatment with prescription drugs (e.g., asthma, epilepsy, hypertension). In addition, new medical problems may develop, or old ones may be exacerbated by pregnancy (e.g., migraine headaches, depression). Studies show that most women who know they are pregnant use either prescribed or over-the-counter drugs during pregnancy (Refs. 13 through 15).

Because pregnant women do use prescription drugs, it is critical that health care providers have access in labeling to available information about the effects of drug exposure in human pregnancies. In the usual case, no human data are available at the time a drug is approved. Animal studies function as a screen for potential human teratogenicity and are a required part of the drug development process. However, the positive and negative

predictive values of animal studies for humans are often uncertain (Ref. 16). In screening for drug-induced fetal effects, animal models can be misleading by suggesting associations that ultimately turn out to be false positive or false negative in humans (Ref. 17). That is, there may be a finding of a drug-associated developmental abnormality in an animal study when that abnormality, or indeed, any abnormality, is not associated with the drug in humans. On the other hand, animal studies may predict that a drug is not associated with any developmental abnormality, while human experience may later indicate that the drug is associated with some developmental abnormality.

In some cases, drugs that are teratogenic in animals when given at high doses are not teratogenic to humans in therapeutic doses, which are typically much lower. In addition, certain animal species are especially disposed to develop a particular type of developmental abnormality (e.g., cleft palate in mice), making it difficult to determine whether drug exposure contributed to the effect or, if so, to what extent. The strongest concordance between animal findings and human effects is when there are positive findings from more than one species, although even in this case the results cannot always be used to predict specific human effects or the incidence in humans (Ref. 18).

Inclusion of clinically relevant new human data in pregnancy labeling is necessary to ensure that labeling complies with the general requirements on content and format of labeling for human prescription drug and biological products (§ 201.56(a)(1) and (a)(2)). Section 201.56(a)(1) provides that the labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug. Section 201.56(a)(2) provides, in part, that ‘‘the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.’’

When 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. For example, animal data available at the time of approval might suggest that use of a particular drug during pregnancy is likely to be associated with a risk for the development of neural tube defects in the fetus. Under the proposed rule, that information would be included in the ''Pregnancy'' subsection of the labeling when the drug is approved. If data developed after the initial approval (perhaps from an appropriately designed and powered pregnancy registry) indicate that the drug may not be associated with neural tube defects in humans, the drug's original labeling—based only on animal data—would be inaccurate, false, and misleading. In such a situation, § 201.56(a) would require that the labeling be updated to include the new information.

f. *Risk conclusions based on human data*. The proposed rule states 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. A risk conclusion based on human data must be followed by a narrative description of the risk(s) as discussed in section IV.B.3.h of this document.

The proposed rule addresses two different situations where human data are available: Those where human data are ''sufficient'' and those involving ''other human data.'' The proposed rule states that ''sufficient human data'' are those that are sufficient to reasonably determine the likelihood that the

drug increases the risk of fetal developmental abnormalities or specific developmental abnormalities. As explained in the proposed rule, sufficient human data may come from such sources as clinical trials, robust pregnancy exposure registries or other large scale, well-conducted epidemiologic studies, or case series reporting a rare event.

The proposed rule provides the following two risk conclusions to be used when human data are sufficient:

- When sufficient human data do not show an increased risk, the risk conclusion must state: ''Human data do not indicate that (*name of drug*) increases the risk of (*type of developmental abnormality or specific developmental abnormality*).'' An example of a hypothetical risk conclusion using this statement is: ''Human data do not indicate that hypothezine increases the risk of structural malformations.'' Another example is: ''Human data do not indicate that hypothezine increases the risk of neural tube defects.''

- When sufficient human data show an increased risk, the risk conclusion must state: ''Human data indicate that (*name of drug*) increases the risk of (*type of developmental abnormality or specific abnormality*).'' An example of a hypothetical risk conclusion using this statement is: ''Human data indicate that theoretamine increases the risk of cardiac abnormalities.'' Another example is: ''Human data indicate that theoretamine increases the risk of hypospadias and clitoral anomalies.'' The proposed rule states that when human data are available but are not sufficient to require the use of one of the two preceding risk conclusions, the likelihood that the drug increases the risk of developmental abnormalities must be characterized as low, moderate, or high. Whether the likelihood of increased risk would be characterized as low, moderate, or high would require a scientific judgment about the quantity and

quality of the available data. For example, if the human data consisted of a pregnancy registry examining the increased risk for a specific developmental abnormality, FDA would consider such factors as the duration of the registry, the number of patients enrolled, and the statistical power of the study to identify or rule out a specified level of risk.

The proposed rule uses a slightly different approach for situations involving other human data,'' i.e., those where the human data are not sufficient to reasonably determine the likelihood that the drug increases the risk of fetal developmental abnormalities or specific developmental abnormalities. As discussed in section II.E of this document, FDA conducted four focus groups to evaluate standard statements being considered by the agency to characterize the increased risk of drug-associated developmental abnormalities in pregnancy labeling. After holding these focus groups, an agency working group further considered numerous possible wordings for standard statements. The working group also prepared many samples of fetal risk summaries to evaluate the concepts being discussed for this proposed rule. These risk summaries were based on varying types and amounts of data and described varying endpoints. The working group's experience in preparing these sample risk summaries indicated that using standardized risk conclusions about human data that were not sufficient to reasonably determine the drug's effect(s) on fetal developmental abnormalities presented difficulties. Using standardized risk conclusions often removed the flexibility needed to accurately convey the data. There were situations where the data did not fit into the format of the standardized risk conclusions. Rather than force the data to fit a standardized risk conclusion, the working group determined that labeling under the proposed rule should not be required to employ

standardized statements when human data are not sufficient. Therefore, the proposed rule would not mandate the use of prescribed sentences when available human data are not sufficient to reasonably determine the drug's effects on fetal developmental abnormalities. Instead, the risk would be classified as either low, medium, or high. FDA seeks 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).''

g. *Risk conclusions based on animal data*. Section 201.56(a)(3) of FDA regulations states that labeling must be based whenever possible on data derived from human experience. Some of the limitations of animal data concerning the increased risk of developmental abnormalities because of drug exposure have been discussed in section IV.B.3.e of this document. There is an additional limitation that the agency considers to be particularly important in determining what conclusions can be drawn from animal data regarding human pregnancy outcomes. Toxic drug exposure may manifest as one type of developmental abnormality (e.g., embryolethality) in an animal species, but a different type of developmental abnormality (e.g., structural anomalies) in humans. Thus, the agency does not believe it is possible to draw a conclusion, based on animal data alone, that a drug is likely to cause an increased risk of a particular type of developmental abnormality (e.g., fetal and infant mortality), much less a specific developmental abnormality (e.g., cleft palate).

However, it is more concerning when teratogenic effects occur in more than one animal species, especially if these effects were consistent across the different species. Accordingly, where the risk conclusion is based solely on animal data, the proposed rule would require that the fetal risk summary component consist only of a risk conclusion, and not, in addition, a description of the effects found in animals. The risk conclusion would be followed by a cross reference to the Data component of the ''Pregnancy'' subsection, and the effects found in animals would be described in the ''Data'' component.

The proposed rule states 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 five risk conclusions.

- When animal data contain no findings for any developmental abnormality, the fetal risk summary must state, ''Based on animal data, (*name of drug*) is not predicted to increase the risk of developmental abnormalities.''

- When animal data contain findings of developmental abnormality but the weight of the evidence indicates that the findings are not relevant to humans (e.g., findings in a single animal species that are caused by unique drug metabolism or a mechanism of action thought not to be relevant to humans; findings at high exposures compared with the maximum recommended human exposure), the fetal risk summary must state, ''Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be low.''

- When animal data contain findings of one or more fetal developmental abnormalities in one or more animal species, and those findings are thought to be relevant to humans, the fetal risk summary must state, ''Based on animal

data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be moderate.''

- When animal data contain robust findings of developmental abnormalities (e.g., multiple findings in multiple animal species, similar findings across species, findings at low exposures compared with the anticipated human exposure) thought to be relevant to humans, the fetal risk summary must state, ''Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be high.''

- When animal data are insufficient to assess the drug's potential to increase the risk of developmental abnormalities, the fetal risk summary must state that fact. When there are no animal data to assess the drug's potential to increase the risk of developmental abnormalities, the fetal risk summary must state that fact.

FDA seeks 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.

h. *Narrative description of the risks*. The proposed rule states that when human data are available, in addition to the risk conclusion(s), the fetal risk summary must be followed by a brief description of the risks of developmental abnormalities as well as on 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 the dose, duration of exposure, or gestational timing of exposure. When appropriate, the description must include the risk above the background risk attributed to drug

exposure. For example, the labeling might state: ''Exposure to Drug X during the first trimester increases the risk of neural tube defects 20-fold, from 10 to 25 defects in 10,000 pregnancies to 200 to 500 defects in 10,000 pregnancies.'' When possible, the description must also communicate the level of certainty about the risk based on the power of the study and confidence limits. Thus, the proposed rule states that, when appropriate, the description must include confidence limits and power calculations to establish the statistical power of the study to identify or rule out a specified level of risk. For example, the labeling might state: ''Compared to a 1.62% prevalence of major malformations in women with the same disease not exposed to the drug, the relative risk of having an affected offspring for Drug X-exposed women is 7.3 (95% CI: 4.4 to 12.2; $p<0.001$).''

i. *Contraindications, warnings, and precautions*. The proposed rule states that if there is information on an increased risk to the fetus from exposure to the drug in the ''Contraindications'' or ''Warnings and Precautions'' sections of the labeling (§ 201.57(c)(5) or (c)(6)), the fetal risk summary must refer to the relevant section.

Section 201.57(c)(5) of FDA's labeling regulations provides that the ''Contraindications'' section must describe ''any situations in which the drug should not be used because the risk of use * * * clearly outweighs any possible therapeutic benefit.'' This requirement applies to the use of a drug in pregnancy. FDA believes that pregnancy is different from other situations, however, in that the risk could be to the fetus as well as to the mother, and that in order to be contraindicated for use in pregnancy, the risk would have to clearly outweigh any possible therapeutic benefit either to the mother or to the fetus. Thus, the risk/benefit analysis would be somewhat different than

for other situations because one would need to consider risk and benefit to both the mother and to the fetus. For example, a drug might have the potential to cause serious harm to the fetus, but be needed by the mother as treatment for an otherwise fatal disease or condition. Given that the mother's death would, depending on the gestational age of the fetus, result in the death of the fetus, the risk to the fetus from the drug would not necessarily outweigh the benefit to the mother.

FDA's understanding is that existing practice has been to contraindicate a drug in its entirety for use in pregnancy if any indication is contraindicated for such use, despite the fact that the risk/benefit analysis might differ for different indications. FDA believes that when there is more than one labeled indication for a drug, a decision should be made separately for each indication as to whether the drug should be contraindicated for use in pregnancy. It may also be appropriate to contraindicate a drug for use in pregnancy only for a particular patient population (e.g., when there is coexisting renal disease). In this case, the labeling should describe specifically the population to which the contraindication applies.

It may also be the case that a drug poses an increased risk to the fetus only during a particular time period, for example, the period of organogenesis or during the third trimester. Thus, the agency believes that if there is a specific known time period when the drug would pose an increased risk to the fetus, the contraindication should specify the time period (e.g., first trimester; after 30 weeks).

Finally, current drug labeling has sometimes contraindicated a drug for use in pregnancy simply because it is reasonable to assume that a pregnant woman would not use or be prescribed that drug. For example, women who

know they are pregnant do not use oral contraceptives or fertility drugs. However, participants at the part 15 hearing clearly emphasized that contraindicating a drug gives the impression that it has been shown to cause fetal developmental abnormalities, perhaps leading women to terminate otherwise wanted pregnancies because of drug exposure before they realized they were pregnant. As was also brought out in the part 15 hearing, health care providers may also recommend termination to pregnant patients when a drug is contraindicated for use in pregnancy. Thus, FDA believes it is not appropriate to contraindicate a drug for use in pregnancy for the sole reason that the drug is not usually prescribed for pregnant women. Rather, a contraindication for use in pregnancy should be based on a determination that the drug should not be used in pregnancy because the risk of use during pregnancy clearly outweighs any possible therapeutic benefit.

4. Clinical Considerations (Proposed § 201.57(c)(9)(i)(D))

The proposed clinical considerations component of pregnancy labeling is intended 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.

a. *Inadvertent exposure*. The agency recognizes that many women are exposed to drugs before they know they are pregnant. Failure to address such inadvertent exposure has been identified as one of the key weaknesses of current pregnancy labeling. Participants in the part 15 hearing advocated that labeling address issues relating to inadvertent exposure because clinical decisions about inadvertent exposures often involve deciding whether to

terminate pregnancies. FDA agrees that it is critical to address inadvertent exposure in labeling. The population at risk for unnecessary terminations due to early drug exposure is large because approximately half of all pregnancies in the United States are unintended (Ref. 1). Thus, the proposed rule would require that the clinical considerations component of pregnancy labeling discuss the known or predicted risks to the fetus from inadvertent exposure, including human or animal data on dose, timing, and duration of exposure. If there are no data to assess the risk from inadvertent exposure, the labeling would be required to state this fact.

b. *Prescribing decisions for pregnant women*. The discussion relating to prescribing decisions for pregnant women would be required to include the following four types of information:

(1) The labeling would be required to describe 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.

There is evidence that women of childbearing age and their health care providers overestimate the likelihood that drugs used in pregnancy will cause serious birth defects, probably because of the thalidomide tragedy in the early 1960s (Refs. 19 through 27). Because of this overestimation of risk, women may not be appropriately treated for serious and even life-threatening diseases or conditions during pregnancy (Refs. 22 and 27). Of the 62 million women of childbearing age (15 to 44) in the United States (Ref. 28), more than 9 million have chronic conditions such as asthma, epilepsy, and hypertension (Ref. 29) that require ongoing treatment with prescription medicines. Failure to treat these conditions properly can have serious consequences for mothers and fetuses (Refs. 25 and 30). The agency believes that including information about

the risks to the pregnant woman and the fetus from the disease or condition to be treated will help health care providers to weigh the risks of drug treatment against the risks of not treating the disease or condition.

(2) The labeling would be required to include information about dosing adjustments during pregnancy. Corresponding information would also be required in the ''Dosage and Administration'' and ''Clinical Pharmacology'' sections (§§ 201.57(c)(3) and (c)(13)). For example, the pregnancy subsection of the labeling might state under ''Clinical Considerations,'' ''Drug X is eliminated more rapidly in pregnant women than in nonpregnant women. Dosage adjustment is necessary for pregnant women. See 'Dosage and Administration.''' If there are no data on dosing in pregnancy, a statement of that fact would be required in the labeling.

Many physiologic changes occur during pregnancy, and these changes can affect drug pharmacokinetics. Assuming that the usual adult dose is appropriate during pregnancy can result in substantial underdosing or, in some cases, excessive dosages. FDA encourages sponsors to conduct studies to determine appropriate dosing during pregnancy. To this end, the agency published a draft guidance for industry on the design, conduct, and interpretation of pharmacokinetic studies in pregnant women. The availability of this guidance entitled ''Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling'' was announced in the **Federal Register** of November 1, 2004 (69 FR 63402).

(3) If use of the drug is associated with maternal adverse reactions that are unique to pregnancy or if known adverse reactions occur with increased frequency or severity in pregnant women, this portion of the labeling would be required to describe such adverse reactions. This description would include,

if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction(s). If information is available on interventions that might be needed, language to that effect would also be required. For example, the labeling might include the following statement: ''Drug X may cause hyperglycemia in pregnant women. Careful monitoring of blood glucose is recommended when using Drug X during pregnancy.''

(4) If it is known or anticipated that treatment of the pregnant woman will cause a complication in the fetus or the neonate, the labeling would be required to describe the complication, the severity and reversibility of the complication, and general types of interventions, if any, that may be needed.

c. *Labor and delivery*. 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 if the drug is expected to affect labor or delivery, the discussion of clinical considerations would be required to provide the 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. FDA believes, for products to which this provision applies, that including this information in the labeling is important to help ensure the safe use of the drug under what may be a common condition of its use. FDA notes that, although the proposed rule would modify slightly the language currently found at § 201.57(c)(9)(ii), these changes are intended solely to update the language used in these sections and not to affect the information required by these provisions to be included in the labeling.

5. Data (Proposed § 201.57(c)(9)(i)(E))

The Data component of the proposed pregnancy labeling is intended to provide a brief overview of the data that are the basis for the fetal risk summary and the clinical considerations portion of the labeling. The discussion of the data is not intended to be all-encompassing, but rather to explain and supplement the conclusions in the fetal risk summary and clinical considerations portions of the labeling.

As in the fetal risk summary portion, the proposed rule states that human and animal data must be presented separately and human data must be presented first. The labeling would be required to describe the studies, including study type(s) (e.g., controlled clinical or nonclinical studies, 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).

Isolated case reports generally would not be included in the Data component of the labeling unless the quality of the report(s) and other factors (e.g., consistency with animal findings; information on the dose, duration, and timing of gestational exposure) support their inclusion.

The proposed rule states that, for human data included in the Data component, 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.

The proposed rule states that, for animal data included in 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

must be described. This proposed requirement addresses the concerns of focus group members and advisory committee members that pregnancy labeling should help health care providers understand the relationship between animal data and human exposures.

FDA seeks comment on whether, in the Data component of labeling, when animal data is described, the rule should also require the inclusion of information on the findings that contribute to the designation of the risk from animal data as low, moderate, or high. For example, should there be information on the number of species with positive findings, the consistency of the findings, or the severity of findings?

C. Lactation Subsection

Proposed § 201.57(c)(9)(ii) would require prescription drug labeling to contain, under the subheading ''8.2 Lactation,'' the following three components: (1) A risk summary, (2) clinical considerations, and (3) data.

1. Risk Summary (Proposed § 201.57(c)(9)(ii)(A))

The proposed rule provides that a lactation risk summary must summarize the following information: (1) The drug's impact on milk production, (2) what is known about the presence of the drug in human milk, and (3) the effects on the breast-fed child. The proposed rule states that when, as discussed below, 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 that the use of the drug is compatible with breast-feeding. Requiring such a statement is supported by FDA's consultation with stakeholders. The discussion at the advisory committee on lactation included a recommendation

that, if appropriate, labeling contain a statement indicating that it is safe for a nursing mother to take a drug. Participants in the September 1997 part 15 hearing also expressed concern that mothers who need to take prescription drugs after they give birth may be advised by their health care providers to choose between breast-feeding and taking a drug. FDA agrees that, if the data support the conclusion, it is important for lactation labeling to indicate that use of a drug is compatible with breast-feeding.

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 impact on milk production, the presence of the drug in human milk, and/or the effects on the breast-fed child, the risk summary would be required to state that fact.

Under FDA's current regulations, information is only required to be included in the ''Nursing mothers'' subsections of FDA's current regulations if a drug is absorbed systemically, in which case, the labeling must contain information about excretion of the drug in human milk and effects on the nursing infant, as well as a description of any pertinent adverse effects observed in animal offspring. FDA believes that if a drug is not absorbed systemically, it is important for the health care provider and the nursing mother to be aware of this fact. Therefore, the proposed rule would require that the labeling of all drugs contain a ''Lactation'' subsection. The proposed rule would require that, when the drug is not systemically absorbed, the risk summary in the ''Lactation'' subsection contain 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 amount of (*name of drug*)

will not be present in breast milk. Breast-feeding is not expected to result in fetal exposure to the drug.''

- *The drug's impact on milk production*. The proposed rule states that the description of the effects of the drug on milk production must include the effect of the drug on the quality and quantity of milk, including milk composition, and the implications of these changes to the milk for the breast-fed child. The advisory committee on lactation thought this information was important and recommended its inclusion in the labeling.

- *The presence of the drug in human milk*. The proposed rule states that the presence of the drug in human milk must be described in one of the following five 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.

If studies demonstrate that the drug is not detectable in human milk, the proposed rule would require that the risk summary state the limits of the assay used.

The advisory committee on lactation recommended that lactation labeling include the amount of drug present in breast milk. Thus, the proposed rule also would require that, if the drug has been detected in human milk, the risk summary must give the concentration detected in milk in reference to a stated adult dose (or, if the drug has been labeled for use in pediatric populations, in reference to the labeled pediatric dose), an estimate of the amount consumed

daily by the infant based on an average daily milk consumption of 150 milliliters (mL) per kilogram (kg) of infant weight per day (Ref. 31), and an estimate of the percent of the adult dose excreted in human milk.

- *Effects on the breast-fed child*. As recommended by the advisory committee on lactation, the proposed rule would require that the labeling contain information regarding the effects of the drug on the breast-fed child. This would include information on the likelihood and seriousness of known or predicted effects on the breast-fed child from exposure to the drug in human milk. As proposed, the risk summary must be 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. For example, the labeling might state: ''Based on its pharmacologic properties, Drug X has the potential to cause sedation in the breast-fed child. However, it is unlikely that sedation will occur because the estimated daily dose in human milk, based on the predicted presence of Drug X in human milk, is 2 percent of the daily pediatric dose for 6- to 12-month old infants.'' If the drug has not been labeled for pediatric use, the amount of the drug predicted to be present in human milk would be stated as a percentage of the maternal (i.e., adult) dose.

2. Clinical Considerations (Proposed § 201.57(c)(9)(ii)(B))

The clinical considerations component of the proposed ''Lactation'' subsection is intended to help health care providers make informed decisions about prescribing drugs for lactating women. The proposed rule would require a discussion of three clinical issues to the extent information on them is available:

- *Minimizing exposure of the breast-fed child*. The proposed rule states that, when there are ways to minimize the exposure of the breast-fed child to the drug, such as timing the dose relative to breast-feeding or pumping and discarding milk for a specified period, the labeling must provide this information.
- *Potential drug effects in the breast-fed child*. The proposed rule states that the labeling must provide 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. For example, the labeling might state: ''Drug X may cause sedation in the breast-fed child.''
- *Dosing adjustment during lactation*. The proposed rule states that, to the extent it is available, information about dosing adjustments during lactation must be provided and that this information must also be included in the ''Dosage and Administration'' and ''Clinical Pharmacology'' sections.

3. Data (Proposed § 201.57(c)(9)(ii)(C))

The proposed rule states that the Data component of the ''Lactation'' subsection must provide an overview of the data that are the basis for the risk summary and the basis for the clinical considerations component.

D. Removing the Pregnancy Category Designation

As discussed in section II.A and II.B of this document, the pregnancy categories currently found in § 201.57(c)(9)(i)(A)(1) through (c)(9)(i)(A)(5) and § 201.80(f)(6)(i)(a) through (f)(6)(i)(e) have been criticized for being overly simplistic and misleading about the degree of risk a drug presents to the fetus. Accordingly, FDA is not including pregnancy categories in its proposed revision to § 201.57. However, the agency believes that it would be confusing to require category designations in the labeling for products subject to § 201.80

while the labeling for products subject to § 201.57 would not contain pregnancy categories. Therefore, the proposed rule would remove the pregnancy category designations (A, B, C, D, and X) from both the headings and text of § 201.80(f)(6)(i)(a) through (f)(6)(i)(e).

V. Implementation Plan for the Proposed Rule

A. General

There are two components to this proposed rule. The first component would require that the labeling of new and recently approved products be revised to comply with the new pregnancy and lactation labeling content (new content) described in proposed § 201.57(c)(9)(i) and (c)(9)(ii). The second component, affecting § 201.80(f)(6)(i), would require products subject to that regulation to remove from existing labeling the pregnancy category designations (e.g., ''Pregnancy Category C'') in both the headings and the text of that subsection of the labeling.

For already approved products subject to the new content requirements, under §§ 314.70(b) and 601.12(f)(1) (21 CFR 314.70(b), 21 CFR 601.12(f)(1)), holders of approved applications would be required to submit a supplement and obtain FDA approval prior to distributing the new labeling. Already-approved products that only would be required to remove the pregnancy category designation would be required to report the change to FDA in an annual report (§§ 314.70(d) and 601.12(f)(3) (21 CFR 314.70(d) and 601.12(f)(3)).

In the following discussion of the implementation plan, the term ''application'' refers to new drug applications (NDAs), biologic licensing applications (BLAs), and efficacy supplements. Any final rule that becomes

effective based on this proposed rule is referred to in the following discussion as ''the pregnancy final rule.''

B. New Content (Proposed § 201.57(c)(9)(i) and (c)(9)(ii))

The new content requirements of the proposed rule would apply to all applications required to comply with FDA's final rule on ''Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products'' (71 FR 3921, January 24, 2006) (the physician labeling rule or the PLR). As stated in § 201.56(b)(1), this includes:

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

The implementation schedule proposed in table 1 of this document would give all affected parties except those who submit an application on or after the date the pregnancy final rule becomes effective a minimum of 3 years after the effective date of the pregnancy final rule to submit labeling with the new content. FDA believes that this 3-year period would give industry sufficient time to use up existing labeling stocks and would avoid requiring manufacturers that have recently made the major labeling revision required by the physician labeling rule to make another significant labeling change in less than 3 years. In addition, the proposed implementation schedule would distribute the number of affected applications requiring review by the agency over a period of several years, thus assisting the agency in managing the workload associated with reviewing the new labeling.

The effective date of the physician labeling rule was June 30, 2006. For ease of coordinating the implementation of the pregnancy final rule with the implementation of the PLR, FDA proposes that the pregnancy final rule would become effective on the first June 30th that occurs at least 120 days after the date of publication of the pregnancy final rule. Thus, if the pregnancy final rule were to publish on January 14, 2010, the rule would become effective on June 30, 2010. Or, if the pregnancy final rule were to publish on June 1, 2010, the rule would become effective on June 30, 2011. For purposes of developing the proposed implementation schedule, FDA has assumed that the pregnancy rule will become effective no earlier than June 30, 2010. If it becomes effective earlier than that, FDA will adjust the implementation schedule accordingly.

Table 1 of this document describes the implementation plan FDA is proposing for the pregnancy final rule.

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
New or Pending Applications:	
Applications submitted on or after the effective date of the pregnancy final rule	Time of submission
Applications pending on the effective date of the pregnancy final rule	4 years after the effective date of pregnancy final rule or at time of approval, whichever is later
Approved Applications Subject to the Physician Labeling Rule:	
Applications approved any time from June 30, 2001, up to and including June 29, 2002, and from June 30, 2005, up to and including June 29, 2007	3 years after the effective date of pregnancy final rule
Applications approved any time from June 30, 2007, up to and including the effective date of the pregnancy final rule	4 years after the effective date of pregnancy final rule
Applications approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of pregnancy final rule

C. Removing the Pregnancy Category (Proposed § 201.80(f)(6))

Holders of applications approved prior to June 29, 2001 (i.e., applications not subject to the PLR), would not be required to implement the new content requirements. 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

pregnancy final rule. Because this is a relatively minor change, FDA believes it is not necessary to stagger its implementation.

VI. Legal Authority

A. Statutory Authority

In this proposed rule, FDA is proposing to revise its regulations prescribing 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.

FDA's revisions to the content and format requirements for prescription drug labeling are authorized by the act and by the Public Health Service Act (the PHS Act). Section 502(a) of the act deems a drug to be misbranded if its labeling is false or misleading ''in any particular.'' Under section 201(n) of the act (21 U.S.C. 321(n)), labeling is misleading if it fails to reveal facts that are material with respect to consequences which 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 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 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 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 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 act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the 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 proposed rule amends the regulations specifying the format and content for such labeling.

Section 351 of the Public Health Service Act (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 proposed requirements for the content and format of the ''Pregnancy'' and ''Lactation'' subsections of labeling for human prescription

drug and biological 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. That analysis is equally applicable to this proposed rule, and we hereby adopt that discussion by reference.

VII. 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.

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs 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 proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because so many prescription drug manufacturers would be affected by the proposed rule, the agency believes that this rule could have a significant impact on a substantial number of small entities. Consequently, the agency

does not certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. The following analysis, in conjunction with the preamble, constitutes the agency's initial regulatory flexibility analysis as required by the Regulatory Flexibility Act.

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 $127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The proposed rule would amend the current requirements for the content of human prescription drug labeling related to use in specific populations. The primary benefit of the proposed rule would be improved communication of clinically relevant information on the safe and effective use of prescription drugs by pregnant or lactating women. Although the agency is unable to quantify these benefits, this proposed rule is the product of over 10 years of consultation with stakeholders. Direct costs of the proposed rule are projected to range from approximately $0.8 million to $17.6 million in any single year, and over 10 years have a total present value of approximately $50.3 million with a 7-percent discount rate or $61.7 million with a 3-percent discount rate. The annualized costs over 10 years would be $7.2 million with both a 7-percent discount rate and with a 3-percent discount rate. Although the agency

is unable to quantify the net benefits of this proposed rule, the rule responds to problems with existing labeling identified by current users of drug product labeling. FDA therefore concludes that the potential benefit of better informed health care providers and patients would justify the costs of the rule. Furthermore, the agency has determined that the proposed rule is not an economically significant rule as defined by the Executive order.

A. Need for the Proposed Rule

In response to concerns about the usefulness of the current ''Pregnancy,'' ''Labor and delivery,'' and ''Nursing mothers'' subsections of prescription drug product labeling, FDA held a part 15 hearing and two advisory committee meetings and consulted with focus groups and the public to solicit comment on how to improve these subsections. During these discussions, participants said that current prescription drug product labeling lacks clarity and often fails to provide meaningful clinical information about drug exposure during pregnancy and lactation. Of equal concern, current prescription drug product labeling is not designed to address either inadvertent drug exposure in early pregnancy or the potential consequences of discontinuing during pregnancy a drug prescribed to the mother to treat a chronic condition. Moreover, the current system of pregnancy categories can be ambiguous, give a false impression of the comparative risks of different prescription drug products, and fail to adequately provide meaningful information that health care providers can use to advise their patients on the safe and effective use of prescription drugs during pregnancy.

This rule, therefore, proposes to improve the quality of prescription drug labeling. Providing up-to-date information on the safe and effective use of prescription drugs during pregnancy and lactation in a standardized format

would make labeling a more reliable resource that health care providers could consult when they seek prescription drug information for their pregnant and lactating patients.

B. Scope of the Proposed Rule

This proposed rule would affect human prescription drugs that would be required to have labeling with a ''Pregnancy'' or ''Lactation'' subsection. Some manufacturers with multiple dosage forms, dosage strengths, and package sizes of the same active ingredients may produce a single version of the labeling to use with all products. Nevertheless, for this analysis, FDA assumes that manufacturers will produce separate labeling for each dosage form, but will use the same version for all package sizes and dosage strengths of the same dosage form. This assumption may lead to an overestimation of the costs of the proposed rule.

C. Costs of the Proposed Rule

The extent to which the proposed rule might affect labeling depends on whether an affected application is subject to the PLR. The labeling for applications subject to the PLR would need to conform to the proposed content requirements for the ''Pregnancy'' and ''Lactation'' subsections of the ''Use in Specific Populations'' section of the full prescribing information (proposed §§ 201.57(c)(9)(i)-(c)(9)(ii)). The labeling of applications not subject to the PLR would only need to conform to the proposed requirement to remove the pregnancy category if it exists. The level of effort required to comply with the proposed changes, therefore, would depend on whether the affected application is subject to the requirements of the PLR. In the analysis of costs, multiple applications for the same prescription drug product are counted only once.

1. Affected Applications

a. *Future applications*. NDAs, BLAs, and efficacy supplements submitted on or after the effective date of the pregnancy labeling final rule are future applications. Even though the number of future applications is unknown, for the analysis of impacts for the PLR (71 FR 3922 at 3969), FDA examined approvals from 1997 to 2001 to estimate the average annual number of applications that might be submitted in the future (i.e., after the effective date of the PLR). An updated analysis of the FDA approval data suggests that these estimates remain representative of current activity. Thus, FDA continues to use the numbers derived for the PLR analysis as the agency's best estimate of future activity. Table 2 of this document shows that manufacturers might submit an estimated 1,580 applications in the 10 years following the effective date of the pregnancy labeling final rule, with approximately 75 percent of these submissions being for innovator products.

b. *Approved or pending applications subject to the PLR*. Any approved or pending application subject to the requirements of the PLR would also need to conform to the requirements of this proposed rule. This includes applications pending on the effective date of the pregnancy labeling final rule and those applications approved between June 30, 2001, and the effective date of the pregnancy labeling final rule. For the purposes of this analysis, FDA assumes that the pregnancy labeling final rule would become effective on June 30, 2010, and affect some applications counted as future applications in the PLR analysis.

This analysis uses FDA's approval data to tally the number of affected approvals between June 30, 2001, and June 30, 2006. This number provides a partial estimate of the number of approved or pending applications that

might be affected by the proposed rule. Because the number of applications that would be submitted between June 30, 2006, and the effective date of the pregnancy labeling rule is unknown, FDA uses the estimate of the number of future applications in years 5 to 10 from the PLR analysis to complete the estimate of the number of approved or pending applications subject to the PLR that might be affected by this proposed rule.

To minimize the burden on industry, FDA proposes that manufacturers with labeling that already conforms to the PLR requirements on the effective date of the pregnancy labeling final rule would have from 3 to 5 years to revise labeling to conform to the requirements of the rule. Table 2 of this document shows that the existing labeling of an estimated 1,300 innovator applications and 600 generic applications would need to be revised to add the new content that would be required by the pregnancy labeling final rule.

TABLE 2.—ESTIMATED NUMBER OF APPLICATIONS SUBJECT TO THE PLR[1]

Year	Future Applications		Pending or Recently Approved Applications		Total	
	Innovator Drugs	Generic Drugs	Innovator Drugs	Generic Drugs	Innovator Drugs	Generic Drugs
1	140	40	0	0	140	40
2	130	40	0	0	130	40
3	120	40	380	260	500	300
4	120	40	480	130	600	170
5	120	40	440	210	560	250
6	110	40	0	0	110	40
7	110	40	0	0	110	40
8	110	40	0	0	110	40
9	110	40	0	0	110	40
10	110	40	0	0	110	40
Total	1,180	400	1,300	600	2,480	1,000

[1] Numbers include an estimated 1,613 pending or future applications (Source: See ANDAs, efficacy supplements, new NDAs and BLAs for years 5 to 10 of table 14 in 71 FR 3922 at 3977 through 3978), and 1,900 approved applications when the pregnancy labeling final rule becomes effective (Source: Analysis of approvals from June 29, 2001, to June 30, 2006, using FDA's approval data). Numbers may not sum due to rounding.

c. *Approved applications not subject to the PLR.* The proposed rule would require that manufacturers responsible for the labeling of approved applications not subject to the requirements of the PLR make minor revisions to remove the pregnancy category from the existing ''Pregnancy'' subsection

of the ‘‘Precautions’’ section of the labeling. Manufacturers would have 3 years after the effective date of the pregnancy labeling final rule to make this change. This provision of the proposed rule would affect any approved application not subject to the PLR that currently has labeling that contains a pregnancy category. Although the actual number of applications that would be affected by this provision of the proposed rule is uncertain, the recent analysis of FDA’s approval data suggests that the labeling of up to 4,720 existing prescription drug products could be affected in year 3 of the rule. Because the labeling of many older products initially approved before 1979 might not contain a pregnancy category, this estimate is an upper bound. Moreover, it should be noted that manufacturers sometimes voluntarily discontinue marketing older products and might do so before they would be required to remove the pregnancy category. Although the magnitude is uncertain, this natural attrition would likely reduce the number of products that would be affected by the pregnancy labeling final rule.

2. One-Time and Annual Labeling Costs

a. *One-time costs*. The actions required under this proposed rule to create drug product labeling can be divided into two major categories: (1) Collecting and organizing the additional information required by this proposed rule and (2) revising existing labeling to add or remove information. FDA notes that designing the labeling is a routine cost of a new application and would not be attributable to this proposed rule. To conform to the requirements of the proposed rule, manufacturers might spend more time on these actions than they currently spend preparing the ‘‘Pregnancy,’’ ‘‘Labor and delivery,’’ and ‘‘Nursing mothers’’ subsections of the labeling, thus incurring additional labeling costs. Which costs would be incurred by a manufacturer will depend

on when in the product's life cycle the labeling subject to the pregnancy labeling final rule would be required and whether the application is subject to the PLR. For example, manufacturers with future innovator applications would only incur costs to collect and organize the required information because designing labeling is a routine cost of a new application. In contrast, manufacturers required to change existing product labeling would incur both types of costs (i.e., collecting and organizing required information, and revising existing labeling).

i. *One-time costs to collect and organize the new content*. Manufacturers responsible for applications subject to the new content requirements would need to collect and organize the information required for the appropriate subsections of the ''Use in Specific Populations'' section of the labeling. Specifically, the proposed rule would merge the information in the ''Pregnancy'' and ''Labor and delivery'' subsections and revise the ''Nursing mothers'' subsection. The merged subsection would be called the ''Pregnancy'' subsection and would require the following: (1) Information about pregnancy exposure registries, (2) a general risk statement, (3) a fetal risk summary, (4) clinical considerations, and (5) a discussion of data. The proposed rule would rename the ''Nursing mothers'' subsection the ''Lactation'' subsection and require the following: (1) A risk summary, (2) clinical considerations, and (3) a discussion of data.

Under the current system, applicants and FDA review any existing animal and human data and determine the appropriate pregnancy category. Although the proposed rule would no longer require that a drug be assigned to a pregnancy category, preparing the new labeling content might require more time than manufacturers currently spend preparing this part of the product

labeling. FDA personnel have worked with manufacturers on a case-by-case basis to update certain prescription drug labeling to include content similar to the content that would be required by the proposed rule. This experience suggests that for innovator products, a physician or other health care professional might spend up to 10 hours collecting the new information. In addition, regulatory affairs and legal personnel might spend up to 10 hours organizing the information and discussing the new content with FDA. At hourly wage costs of $100 for medical personnel and $50 for regulatory and legal personnel, manufacturers would incur about $1,500 in additional costs (10 hours x $100 per hour + 10 hours x $50 per hour). Because labeling of generic drug products duplicates the labeling of reference listed drugs, FDA anticipates that manufacturers of generic products would not incur these incremental costs.

Furthermore, under § 314.50(l)(1)(i), all manufacturers submitting new or revised prescription drug labeling must prepare an electronic version of the labeling for submission to the agency. Some manufacturers may incur incremental costs to prepare and transmit an electronic version that is consistent with the XML (Extensible Markup Language)-based Structured Product Labeling (SPL) standard. Because FDA has little information on the impact of this step, FDA requests detailed comment from industry on these costs.

ii. *One-time costs to revise existing prescription drug labeling*. The agency has previously estimated that the cost of revising prescription drug labeling varies with the size of the manufacturer (68 FR 6062 at 6074, February 6, 2003). Product labeling involves many departments in a manufacturer, including legal, drug safety, regulatory affairs, layout, and production personnel. Larger

manufacturers with several administrative layers may require more time to change labeling than smaller manufacturers with fewer layers. In addition to labor costs, manufacturers incur material costs for each change to drug product labeling, including artwork and labeling scrap. If the rule were to require a labeling revision without allowing sufficient time to deplete existing inventories of labeling, manufacturers might also lose the value of labeling that they must throw away.

Using 2004 wages, table 3 of this document shows the estimated labor and material costs for generic drug manufacturers and three sizes of innovator manufacturers to revise labeling. Because the proposed implementation schedule would allow manufacturers with approved or pending applications subject to the PLR a minimum of 3 years to revise product labeling to conform to the requirements of the pregnancy final rule, manufacturers are not expected to incur any additional inventory costs beyond scrap. Material costs, therefore, include only the average cost of artwork and scrap.

TABLE 3.—LABELING REVISION COSTS BY SIZE AND TYPE OF MANUFACTURER

Type of manufacturer	Labor Cost ($)	Material Cost ($)	Total Cost ($)
Generic:	1,000	500	1,500
Innovator (estimated share of products):			
Small (5 percent)	1,000	500	1,500
Medium (5 percent)	1,500	1,420	2,920
Large (90 percent)	2,180	2,020	4,200

Source: 68 FR 6062 at 6074, updating for 2004 costs and excluding excess inventory loss from the material costs.

FDA's approval data suggests that large manufacturers with 1,000 or more employees produce about 90 percent of the affected innovator prescription drug products. Assuming a uniform distribution of the other 10 percent of innovator prescription drug products among small and medium-size manufacturers, manufacturers of innovator prescription drug products may incur a weighted average cost of about $4,000 per product to revise existing product labeling ((5 percent small innovator manufacturers x $1,500) + (5 percent medium-size innovator manufacturers x $2,920) + (90 percent large

innovator manufacturers x $4,200)). Generic drug manufacturers may incur about $1,500 per product to revise labeling.

iii. *One-time cost to prepare artwork for prescription drug labeling other than trade labeling*. The PLR requires that trade labeling (labeling on or within the package from which the drug is to be dispensed) be printed in a minimum of 6-point type size and that labeling disseminated in other contexts (nontrade labeling) be printed in a minimum of 8-point type size (§ 201.57(d)(6)). In the analysis of impacts for the PLR, FDA assumed that manufacturers would incur additional costs for nontrade labeling because the 8-point type size requirement would require that manufacturers revise nontrade labeling to accommodate the larger type size. FDA makes the same assumption for prescription drug labeling incorporating the new pregnancy and lactation content: that affected manufacturers would incur additional one-time costs to revise nontrade labeling to accommodate the new pregnancy and lactation content in the 8-point type size. The agency previously estimated it would cost manufacturers about $810 per product to revise and proofread the layout, and to prepare artwork (71 FR 3922 at 3981). Updating for current material and labor costs, on average, FDA estimates that, on average, manufacturers might spend $1,000 for each affected innovator product.

b. *Annual incremental costs to print longer labeling*. Longer labeling increases the cost of paper, ink, and other ongoing incremental printing costs. Some requirements of the proposed rule would increase the length of labeling. The incremental increase will depend on many factors, including the number of animal and human studies that have been conducted and their findings, the known risks of the drug, and whether a pregnancy registry exists. Based on the agency's experience with recent labeling changes incorporating content

similar to that proposed in this rule, labeling conforming to both the PLR and the proposed requirements might increase by approximately 15 square inches in 6-point type size and 24 square inches in 8-point type size.[4] Although the estimate is based on a small number of labeling changes, FDA concludes it reasonably approximates the additional amount of paper that would be needed. Nevertheless, FDA requests comment from industry on these assumptions.

i. *Trade labeling*. Manufacturers must send trade labeling with all shipments of prescription drugs and with any samples distributed to health care providers. The PLR requires that trade labeling be printed in a minimum of 6-point type size. The proposed new content requirements would increase the size of trade labeling by an estimated 15-square inches. To conserve space, trade labeling is normally printed on both sides of the paper. The proposed new content, therefore, would add about 7.5-square inches of paper to the overall size of trade labeling. The agency previously estimated that manufacturers would spend about $0.0086 to produce 100-square inches of labeling (65 FR 81082 at 81107). Updating for inflation, FDA estimates that manufacturers might spend $0.01 for each additional 100-square inches of labeling they produce.

The agency has also previously estimated that, on average, manufacturers annually send up to 650,000 pieces of trade labeling with each innovator product and up to 370,000 pieces of trade labeling with each generic product.

[4] This estimate is based on the agency's sample labeling in the appendix, experience with recent case-by-case labeling changes, and the results of a study on new approvals between January 1, 1997, and December 31, 2002. The net increase in the number of characters was tallied for each case and for the hypothetical samples in the appendix. Using the average increase in the number of characters and the proportion of drug products for each pregnancy category, we estimate that prescription drug labeling could increase by a weighted average of 3,200 characters. Labeling can accommodate approximately 200 characters per square inch in 6-point type size and about 130 characters per square inch in 8-point type size. Therefore, 3,200 additional characters would require about 15-square inches of paper in 6-point type size and 24-square inches of paper in 8-point type size.

In addition, industry wide, a total of 90 million pieces of trade labeling are distributed with drug samples each year (71 FR 3922 at 3979). Because the new content provisions of this proposed rule would only add about 7.5-square inches to the overall size of trade labeling, the cost of labeling for an affected innovator product would increase by approximately $470 each year (650,000 pieces per product x $0.000096 per square inch x 7.5-square inches per piece). Generic drug manufacturers would incur annual incremental printing costs of about $280 for each generic product affected by the proposed rule (370,000 pieces per product x $0.000102 per square inch x 7.5-square inches per product).

FDA assumes that almost all samples are innovator products. Although it is unlikely that all samples would be affected by the proposed rule, the annual cost of longer trade labeling accompanying all samples of innovator products could equal about $65,000 (90 million samples x $0.000096 per square inch x 7.5-square inches per piece).

ii. *Nontrade labeling*. The PLR requires that any nontrade labeling be printed in a minimum of 8-point type size. For applications subject to the PLR, the new content requirements of the proposed rule would increase the size of the paper needed to print nontrade labeling by approximately 24 square inches. FDA assumes that only innovator products would incur these costs because almost all nontrade labeling is for innovator products. The agency previously estimated that manufacturers might distribute to health care providers and consumers an annual average of 730,000 pieces of labeling during the first 3 years of the life of an innovator product (71 FR 3922 at 3981). FDA assumes that this estimate is also a reasonable estimate of the number of pieces of labeling that would be distributed in the first 3 years after a

product is relabeled under this rule. Thus, a manufacturer might spend up to $5,100 per innovator product to print labeling in 8-point type size.[5]

iii. *Physicians' Desk Reference (PDR) costs*. The new content requirements of this proposed rule would add about 0.2 page to labeling printed in the PDR and would cost manufacturers an additional $2,350 annually for each affected product.[6] FDA assumes that these costs would be incurred by the pharmaceutical industry as fees paid to the publisher of the PDR. The total cost for a manufacturer to print longer labeling in the PDR depends on how many years the labeling remains in the PDR. In the economic analysis of the PLR, FDA assumed that only 75 percent of the affected innovator products would have labeling published in the PDR (some smaller manufacturers do not publish labeling in the PDR) and would continue to include the labeling in the PDR in subsequent years (71 FR 3922 at 3976). FDA makes the same assumptions for this analysis.

3. Summary of Industry Compliance Costs for the Proposed Rule

a. *One-time costs for applications subject to the PLR*. Manufacturers with future innovator applications or those with innovator applications pending on the effective date of the pregnancy labeling rule would incur one-time costs to collect and organize the information required for prescription drug labeling conforming to the rule, but would not incur one-time costs to revise existing

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[5] For the PLR, the agency estimated that manufacturers would print and distribute 775,000 pieces of labeling in 8-point type size in the first year of the life cycle of an innovator drug product and 710,000 pieces in years 2 and 3. Compared to the 6-point type size, about 59 percent more paper would be needed to print the new content in 8-point type size. Printing on one side of the paper, manufacturers would need about 24 square inches more paper to accommodate the new content. For this analysis, manufacturers would spend about $5,100 per product to print longer labeling ((775,000 + 710,000 + 710,000) x $0.000096 per sq inch x 24 sq inches = $5,083).

[6] There are approximately 15,850 characters on an average page of the PDR. The new content adds, on average, 3,200 more characters, requiring an additional 0.2 page. Using the lowest per page cost shown on the 2006 PDR rate card, manufacturers might spend up to $2,350 per product to add the new content ($11,730 per page x 0.2 page).

labeling. As explained in section VIII.C.2.a.i of this document, FDA estimates that manufacturers would spend approximately $1,500 to collect and organize the information for the new pregnancy and lactation content. In contrast, manufacturers with future generic applications would incur no additional costs.

Manufacturers with applications approved on or after June 30, 2001, up to and including the effective date of the pregnancy labeling final rule, would incur costs to collect and organize the new content information and to revise existing prescription drug labeling. As described in section VIII.C.2.a.ii of this document, the estimated average cost to revise existing labeling equals $1,500 for generic drugs and $4,000 for innovator drugs. Moreover, manufacturers with innovator products might incur another $1,000 to prepare the artwork for labeling not accompanying the prescription drug product. Therefore, manufacturers might spend a total of $6,500 for existing innovator labeling ($1,500 to gather and organize information for the new content + $4,000 to revise trade labeling + $1,000 to prepare artwork for labeling not accompanying the prescription drug product) and a total of $1,500 for existing generic labeling.

Table 4 of this document shows that total one-time labeling costs would be $11.1 million and range from $0.2 million to $3.5 million in any single year. As shown in table 2 of this document, after 10 years, the labeling of approximately 2,480 innovator drug products and about 1,000 generic drug products would include the new pregnancy and lactation content.

TABLE 4.—ONE-TIME COSTS TO PREPARE NEW CONTENT AND REVISE EXISTING LABELING FOR APPLICATIONS SUBJECT TO THE PLR[1]

Year	One-Time Costs ($ million)		
	Innovators	Generic	Total
1	0.2	0.0	0.2

TABLE 4.—ONE-TIME COSTS TO PREPARE NEW CONTENT AND REVISE EXISTING LABELING FOR APPLICATIONS SUBJECT TO THE PLR[1]—Continued

Year	One-Time Costs ($ million)		
	Innovators	Generic	Total
2	0.2	0.0	0.2
3	2.7	0.4	3.0
4	3.3	0.2	3.5
5	3.0	0.3	3.4
6	0.2	0.0	0.2
7	0.2	0.0	0.2
8	0.2	0.0	0.2
9	0.2	0.0	0.2
10	0.2	0.0	0.2
Total	10.2	0.9	11.1

[1] Costs may not sum due to rounding. See table 2 of this document for details on the number and distribution of affected products.

b. *Annual incremental printing costs for applications subject to the PLR.*

i. *Trade labeling.* As described in section VIII.C.2.b.i of this document, the agency estimates that each year manufacturers print an average of about 650,000 pieces of trade labeling for each innovator product and an average of about 370,000 pieces of trade labeling for each generic product. Based on the average number of pieces of trade labeling and the estimated number of affected applications subject to the PLR from table 2 of this document, table 5 of this document shows the cumulative number of pieces of trade labeling that would be affected by this proposed rule.

TABLE 5.—CUMULATIVE NUMBER OF PIECES OF PRESCRIPTION DRUG TRADE LABELING BY TYPE OF PRODUCT FOR APPLICATIONS SUBJECT TO THE PLR[1]

Year	Cumulative Number of Pieces (million)		
	Innovator	Generic	Samples
1	90	10	90
2	180	30	90
3	500	140	90
4	890	200	90
5	1,250	300	90
6	1,330	310	90
7	1,400	330	90
8	1,470	340	90
9	1,540	360	90
10	1,610	370	90

[1] Numbers may not sum due to rounding. The cumulative calculation assumes that manufacturers print 650,000 pieces for each innovator product and 370,000 pieces for each generic product, and once a product is approved, it remains on the market for the entire analysis.

Printing longer trade labeling would cost manufacturers a total of $9.9 million over 10 years, including $7.4 million for innovator trade labeling, $1.8 million for generic trade labeling, and $0.7 million for trade labeling accompanying samples. As shown in table 6 of this document, annual costs to print the additional information that would be required by this proposed rule range from $0.1 million in year 1 to $1.5 million in year 10. However, if at some point in the future, manufacturers can supply trade labeling electronically, the rule will cease to impose these annual incremental printing costs.

TABLE 6.—ANNUAL INCREMENTAL PRINTING COSTS FOR LONGER TRADE LABELING[1]

Year	Costs by Type[2] ($ million)			
	Innovator	Generic	Samples	Total
1	0.1	0.0	0.1	0.1
2	0.1	0.0	0.1	0.2
3	0.4	0.1	0.1	0.5
4	0.6	0.2	0.1	0.9
5	0.9	0.2	0.1	1.2
6	1.0	0.2	0.1	1.3
7	1.0	0.2	0.1	1.3
8	1.1	0.3	0.1	1.4
9	1.1	0.3	0.1	1.5
10	1.2	0.3	0.1	1.5
Total	7.4	1.8	0.7	9.9

[1] Costs may not sum due to rounding.
[2] Manufacturers would incur printing costs of about $72.37 for every 100,000 pieces of innovator trade labeling and about $76.58 for every 100,000 pieces of generic trade labeling. Trade labeling accompanying prescription drug samples would cost industry about $65,132 annually. See section IX.C.2.b.i of this document for details.

ii. *Nontrade labeling*. As discussed in section VIII.C.2.b.ii of this document, the new content requirements of the pregnancy labeling final rule likely would require manufacturers to print longer nontrade labeling in 8-point type size during the first 3 years after adding the new content to labeling. FDA assumes that only innovator products would incur these costs because almost all nontrade labeling is for innovator products. Thus, over 10 years, manufacturers of innovator products might spend up to $12.6 million ($5,100 per innovator product x 2,480 innovator products) to print labeling in 8-point type size.

iii. *Physicians' Desk Reference*. As discussed in section VIII.C.2.b.iii of this document, manufacturers of innovator products may pay an additional $2,350 annually to include longer prescription drug labeling in the PDR. Because FDA assumes that, after the first year, labeling would remain in the PDR for all subsequent years, PDR printing costs are cumulative. As illustrated in table 7 of this document, in 10 years industry might incur a cumulative total of $27.8 million to print longer labeling in the PDR.

TABLE 7.—CUMULATIVE NUMBER OF AFFECTED APPLICATIONS AND ANNUAL INCREMENTAL COST OF LONGER LABELING PRINTED IN THE PDR[1]

Year	Cumulative Number of Affected Innovator Applications[2]	Annual Incremental Cost ($ mil)
1	110	0.2
2	210	0.5
3	590	1.4
4	1,040	2.4
5	1,460	3.4
6	1,540	3.6
7	1,620	3.8
8	1,700	4.0
9	1,780	4.2
10	1,860	4.4
Total Cost	27.8	

[1] Costs may not sum due to rounding.
[2] Seventy-five percent of innovator products adding new content (see table 2 of this document) would be included in the PDR.

c. *One-time costs for applications not subject to the PLR*. The proposed rule would require that manufacturers with approved prescription drugs not subject to the PLR remove the pregnancy category from labeling if a category exists. To minimize the impact on industry, the agency proposes to give manufacturers 3 years after the effective date of the pregnancy labeling final rule to make these changes. The proposed implementation schedule would give manufacturers sufficient time to deplete their stocks of labeling. Because removing the pregnancy category is a minor labeling change, manufacturers not subject to the PLR would only need to submit revised labeling with their annual reports. In most cases, the burden on manufacturers would be less than

the average standard costs to revise existing labeling (see table 3 of this document). However, some manufacturers with multiple applications not subject to the PLR may need to revise simultaneously the labeling of many products, creating other costs than those estimated for standard labeling revisions. FDA requests detailed comment from industry about the potential burden of the implementation schedule for this provision of the proposed rule.

Based on an analysis of FDA's approval data, an estimated 4,720 prescription drug products would be affected by this provision of the proposed rule. The agency estimates that in year 3, manufacturers would remove the pregnancy category from labeling of 1,700 innovator prescription drug products and 3,020 generic prescription drug products, at a total cost of $11.3 million ((1,700 innovator products x $4,000 per innovator product) + (3,020 generic products x $1,500 per generic product)). This estimate likely overstates the direct compliance costs because many companies would remove the pregnancy category at the same time they voluntarily revise product labeling for other reasons.

d. *Summary of compliance costs*. The industry compliance costs of the proposed rule include the following: (1) One-time cost to prepare the new ''Pregnancy'' and ''Lactation'' subsections of trade labeling and labeling not accompanying prescription drug products, and (2) annual incremental costs to print longer labeling.

Similar to the rollout for PLR, FDA would provide training to medical reviewers on the requirements of the final pregnancy labeling rule. Nevertheless, reviewing the new labeling, including the longer content, would increase the review times and workloads of medical reviewers in the review

divisions. Because the long-term impact of the rule depends on a number of uncertain factors, we are unable to quantify this burden on the agency.

As shown in table 8 of this document, the total present value of all costs equals $50.3 million with a 7-percent discount rate or $61.7 million with a 3-percent discount rate. The annualized cost would be $7.2 million with both a 7-percent discount rate and a 3-percent discount rate.

TABLE 8.—SUMMARY OF COMPLIANCE COSTS[1]

Year	One-time Costs ($ mil)	Annual Costs ($ mil)	Total Costs ($ mil)	Present Value ($ mil)	
				3%	7%
1	0.2	0.6	0.8	0.8	0.8
2	0.2	1.2	1.3	1.3	1.2
3	14.4	3.2	17.6	16.1	14.4
4	3.5	5.4	8.9	7.9	6.8
5	3.4	7.4	10.8	9.3	7.7
6	0.2	7.0	7.1	6.0	4.7
7	0.2	6.4	6.6	5.3	4.1
8	0.2	5.9	6.1	4.8	3.5
9	0.2	6.2	6.3	4.9	3.5
10	0.2	7.0	7.1	5.3	3.6
Total	22.5	50.3	72.7	61.7	50.3

[1] Costs may not sum due to rounding.

D. Benefits

This proposed rule is part of the agency's ongoing efforts to improve the quality of prescription drug labeling. To effectively communicate information about a drug, labeling should be easily accessible, understandable, accurate, reliable, and up-to-date. The agency's public health initiative to provide labeling in an electronic format is intended to make labeling accessible. This proposed rule would address the other aspects of effective communication and result in better quality prescription drug labeling. Once a prescription drug is approved, information starts to become available regarding clinical experience on the use of the drug during pregnancy or lactation. The purpose of this proposed rule is to ensure that prescription drug labeling includes any

available clinical information that can inform health care providers about the safe and effective use of prescription drugs during pregnancy and lactation. By requiring that manufacturers update prescription drug labeling with clinically relevant information, the proposed rule would improve the quality of labeling and could lead to better informed health care providers. The agency is unable to quantify the potential benefits of the proposed rule, but expects that better quality information in prescription drug labeling has the potential to improve the advice that health care providers give women about the safe and effective use of prescription drugs during pregnancy and lactation.

1. Current Use of Prescription Drugs.

a. *Women of reproductive age*. Many women between 15 and 44 years of age take prescription drugs. Data from the Medical Expenditure Panel Survey (MEPS) show that, in 2003, almost 70 percent of the women of reproductive age were prescribed at least one prescription drug (Ref. 32). Moreover, in a recent survey of medication use in adults, 82 percent of the women between 18 and 44 years of age reported using some type of medication in the week preceding the survey and 46 percent of these women reported using at least one prescription drug (Ref. 9).

b. *Pregnant women*. A recent retrospective study of over 150,000 pregnant women enrolled in 8 health maintenance organizations located throughout the United States found that within 270 days before delivery, over 60 percent of the women included in the study were dispensed a prescription drug other than a vitamin or mineral supplement (Ref. 33). Oral anti-infective drugs were the most commonly dispensed prescription drugs, accounting for about 40 percent of all dispensed drugs. Even though almost half of the pregnant women in this study received prescription drugs with pregnancy category A or B, over

30 percent received prescription drugs with pregnancy category C, and 2 percent received category D or X drugs (excluding female reproductive hormones). Similarly, a smaller study of rural obstetric patients in West Virginia found that, excluding prenatal vitamins and minerals, about 60 percent of the pregnant women in the study were prescribed a prescription drug (Ref. 34). Although this study did not examine the pregnancy category of the prescribed drugs, antibiotics were the most frequently prescribed type of drug.

These newer findings support findings reported in a 1994 Institute of Medicine report on women in clinical trials (Ref. 35). The report cited two studies from the 1980s on prescription drug use by pregnant women. One study found that pregnant women took an average of 3.8 medications and the other found that over 75 percent of pregnant women took 3 to 10 drugs during their pregnancy. Studies of pregnant women in several developed countries have found similar results for prescription drug use during pregnancy (Refs. 14, 36, and 37).

c. *Lactating women*. There is less information about the effect of prescription drugs on lactation than about effects on pregnancy. The percentage of new mothers who breast-feed their newborns continues to grow. A recent study found that the percent of mothers who breast-feed their newborns at some time increased from about 50 percent in 1990 to about 70 percent in 2003 (Ref. 38). With improved labeling, health care providers would have more concise clinical information about the use of prescription drugs during lactation, allowing women to make more informed choices about continuing to nurse their newborns while taking prescription drugs.

2. Current Pregnancy Labeling Is Not Adequate

Since 1979, most human prescription drug product labeling includes ''Pregnancy,'' ''Labor and delivery,'' and ''Nursing mothers'' subsections. Besides providing information about a prescription drug's effect on reproduction, pregnancy, and the development of the fetus, each ''Pregnancy'' subsection must include a letter category (A, B, C, D, or X) intended to: (1) Communicate the prescription drug's reproductive and developmental risks or (2) weigh the risks and potential benefits of the prescription drug. The pregnancy letter category suggests increased risk as the letters ascend and equivalent risk for drugs with the same letter. This is a particular problem with category C because a prescription drug can be assigned this category when sponsors: (1) Lack both animal and human data or (2) have adverse animal data, but lack human data.

Pregnant women are rarely included in premarket clinical trials unless a drug is being developed to treat a condition unique to pregnancy. Consequently, few sponsors have any premarket data from pregnant women. Because human data on use during pregnancy are rarely available when a prescription drug is initially approved, category C is the most frequently assigned category. For example, a survey in the early 1990s found that about two-thirds of all prescription drugs in the hardcopy version of the PDR were in category C (Ref. 39). A recent search of the electronic PDR supports this observation. The study also found that over 60 percent of the prescription drugs with a pregnancy category were in category C (Ref. 40). Furthermore, once approved, prescription drugs tend to retain their initial pregnancy category.

Current labeling fails to provide up-to-date information about prescription drug use by pregnant or lactating women. Since the 1990s, the Teratology Society and health care providers have called for the agency to replace the current pregnancy categories with narrative statements that summarize and interpret all available human data.

3. Potential Benefits From Better Quality Labeling

As described in sections II and III of this document, FDA has consulted extensively with stakeholders interested in the use of prescription drugs during pregnancy and lactation. This proposed rule is in part a result of those consultations and would ensure that labeling contains clinically relevant information about prescription drug use during pregnancy and lactation to help health care providers and their patients make informed decisions about their treatment options. Although FDA has little information about adverse outcomes related to incomplete labeling information, better informed decisions about treatment options would likely lead to better outcomes.

a. *Treatment of chronic diseases during pregnancy or while lactating*. Improved information about the safe and effective use of prescription drugs during pregnancy would benefit health care providers and their patients who are pregnant and require medication to treat chronic diseases. The number of women who may benefit from better informed health care providers depends on many factors, including the prevalence of chronic diseases in pregnant women. Some chronic diseases (such as asthma, diabetes, hypertension, mental illness, and epilepsy) may result in negative health outcomes if left uncontrolled during pregnancy and lactation. Without adequate information, women with chronic medical conditions may receive suboptimal treatment, and suboptimal treatment may lead to poor health outcomes for the woman

and her fetus. By requiring that manufacturers include human data, labeling will become a reliable source of up-to-date information on prescription drug use during pregnancy. Without complete information about the benefits and risks of continuing medications during pregnancy, women with chronic medical conditions cannot make informed decisions about whether to stop taking their prescription drugs during pregnancy, and could take actions that might jeopardize their health or the health of their fetuses (Ref. 41).

i. *Pregnancy and asthma*. An estimated 6 million women of reproductive age have asthma. Previous studies have found that from 4 to 7 percent of pregnant women have asthma (Ref. 42); a recent study that used data from national health surveys conducted from 1997 to 2001 found that the annual prevalence of current asthma in pregnant women ranged from 3.7 to 8.4 percent (Ref. 43). Uncontrolled asthma has been associated with negative outcomes for both the pregnant women and the fetus.

ii. *Other chronic conditions*. The Centers for Disease Control and Prevention (CDC) tracks live births for women with several medical risk factors, including some chronic conditions requiring prescription drug therapy. For example, in 2003, of the approximately 4 million live births, some of the most frequent maternal risk factors included diabetes (3.3 percent), cardiac disease (0.5 percent), chronic (not pregnancy-related) hypertension (0.9 percent), and pregnancy-related hypertension (3.7 percent) (Ref. 44). Moreover, it has been reported that about 1 million women of reproductive age have epilepsy (Ref. 45) and up to 9 percent of pregnant women may experience depression (Ref. 46).

b. *Managing inadvertent exposure to drugs*. Improved information about the effects of inadvertent exposure to prescription drugs before women know

they are pregnant would help health care providers to advise these women about the consequences of their inadvertent exposure. Because about one-half of the pregnancies in the United States are unintended, many women are taking prescription drugs before they are aware of the pregnancy (Ref. 41). Inadvertent exposure to prescription drugs during pregnancy may be of particular concern for women taking prescription drugs for chronic conditions. Fears about possible fetal harm from early exposure to prescription drugs can create anxiety for pregnant women and their families.

c. *Use of OTC drugs and dietary supplements by pregnant women*. Some studies in the United States have found that pregnant women often take over-the-counter (OTC) drugs and dietary supplements (Refs. 34, 47, and 48). It is possible that women are substituting these products for prescription drugs because OTC drugs and dietary supplements are perceived as being safer for use during pregnancy than prescription drugs. However, information on the safety of many of these products during pregnancy is as limited, if it is available at all, as that for prescription drugs. Furthermore, unlike prescription and OTC drugs, dietary supplements can be marketed without FDA premarket approval. Providing up-to-date information on the risks and benefits of prescription drugs may encourage more pregnant and lactating women to use safe and effective products that they might otherwise avoid.

4. Potential Benefits for Companies in the International Market

Besides the potential public health benefit of better informed health care providers, the proposed rule may benefit individual manufacturers operating on a global scale. In 1979, the United States began requiring that prescription drug manufacturers include a pregnancy category in the labeling of any systemically absorbed prescription drug. Although many European countries

adopted similar category systems, recent guidance from the European Medicines Agency (EMEA) requires that prescription drug labeling include a narrative risk statement rather than a pregnancy category (Ref. 49). FDA's proposed rule would require narrative risk statements similar to those required by the EMEA. More consistent labeling at an international level may create some efficiency gains for global manufacturers marketing prescription drugs in both the United States and the European Union. FDA does not attempt to quantify these potential gains in efficiency.

E. Impacts on Small Entities

1. The Need for, and the Objectives of, the Proposed Rule

The current labeling for pregnant and lactating women provides limited clinical information for health care providers and their patients. The use of pregnancy categories is confusing and can be misinterpreted. The primary objective of the proposed rule is to modernize the content of the ''Pregnancy,'' ''Labor and delivery,'' and ''Lactation'' subsections of prescription drug product labeling and replace the category system with a narrative summary of potential risk. Narrative information can provide a valuable resource to clinicians and their patients about the relative risks and benefits of prescription drug use during pregnancy and lactation.

2. Description and Estimate of the Number of Small Entities Affected

This proposed rule would affect all small entities with applications required to include ''Pregnancy'' and ''Lactation'' subsections in the labeling. The Small Business Administration (SBA) considers Pharmaceutical Preparation Manufacturing firms (NAICS (North American Industry Classification System) 325412) with fewer than 750 employees and Biological

Product Manufacturing firms (NAICS 325414) with fewer than 500 employees to be small entities. The U.S. Census Bureau reports that in 2002 there were 296 biological product manufacturing establishments (Ref. 50) and 901 pharmaceutical preparation manufacturing establishments (Ref. 51). However, Census employment size classes for pharmaceutical preparation manufacturing do not correspond to SBA size categories. For this analysis, any pharmaceutical preparation manufacturing establishment with less than 1,000 employees would be considered a small entity. Census data suggest that approximately 96 percent of biological product manufacturing establishments and no more than 97 percent of the pharmaceutical preparation manufacturing establishments could be considered small entities. Despite the large number of small entities, large companies manufacture most prescription drug products.

Because the labeling of all prescription drugs required to have a pregnancy category would be affected by the pregnancy labeling final rule, the agency expects this rule to have an impact on a substantial number of small entities. An analysis of FDA's approval data shows that about 60 small or privately held entities would be required to revise existing prescription drug labeling to conform to the content requirements between year 3 and year 5 of the proposed rule. An additional 180 small or privately held entities would be required to remove the pregnancy category from existing prescription drug labeling within 3 years of the effective date of the pregnancy labeling final rule, and many of these small entities would be required to remove the pregnancy category from more than 10 existing products. Because some of these entities would be required to make several labeling changes in the same

year, the agency requests detailed comment from affected small entities on the potential burden of the proposed rule.

The compliance requirements for small entities under this proposed rule are the same as those described above for other affected entities. Compliance primarily involves revising subsections of prescription drug labeling to conform to the requirements of the proposed rule. Because manufacturers already submit labeling to FDA, no additional skills would be required to comply with the proposed rule. The small entities likely to bear the highest total costs under this proposed rule are those entities that would need to simultaneously revise the prescription drug labeling of several high-volume products. Because these small entities would likely have the highest sales volumes of affected products manufactured by small entities, the incremental cost per unit sold is likely to be relatively low. In contrast, small entities with a single, low-volume product would have a higher incremental cost per unit sold. The following examples illustrate possible impacts on small entities with different production volumes. Prescription drug labeling costs are estimated for a small entity that must revise labeling of an innovator product. Table 9 of this document outlines the projected per-unit and total costs to the entity with three different levels of production: 1,000, 10,000, and 100,000 units produced per year.

TABLE 9.—ESTIMATED COSTS FOR HYPOTHETICAL SMALL ENTITY WITH A SINGLE INNOVATOR PRODUCT, UNDER THREE ALTERNATIVE LEVELS OF PRODUCTION[1]

Cost Category	Number of Units Produced and Sold Each Year		
	100,000	10,000	1,000
One-Time Costs:[2]			
Add new content to existing trade labeling	$5,420	$5,420	$5,420
Prepare labeling not accompanying prescription drug products	$5,100	$5,100	$5,100
Total One-Time Costs	$10,520	$10,520	$10,520
Annual Incremental Costs:			
Printing longer trade labeling[3]	$80	$8	$1
Printing longer PDR[4]	$2,350	$2,350	N/A
Total Annual Incremental Costs	$2,430	$2,358	$1

TABLE 9.—ESTIMATED COSTS FOR HYPOTHETICAL SMALL ENTITY WITH A SINGLE INNOVATOR PRODUCT, UNDER THREE ALTERNATIVE LEVELS OF PRODUCTION[1]—Continued

Cost Category	Number of Units Produced and Sold Each Year		
	100,000	10,000	1,000
Annualized Costs:[5]			
Total Annualized Costs at 3 percent	$3,660	$3,590	$1,230
Additional annualized cost per unit sold at 3 percent	$0.04	$0.36	$1.23
Total Annualized Costs at 7 percent	$3,920	$3,850	$1,500
Additional annualized cost per unit sold at 7 percent	$0.04	$0.39	$1.50

[1] Numbers may not sum due to rounding.
[2] Includes one-time costs to collect and organize information for the new content ($1,500), revise trade labeling ($2,920; see Medium firm in table 6 of this document), prepare artwork for labeling in 8-point type size ($1,000), and print labeling in 8-point type size to distribute directly to health care providers.
[3] Number of pieces of trade labeling printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $0.0005 per piece.
[4] Assumes that products with less than 10,000 units per year will not have labeling in the PDR.
[5] One-time costs are annualized over 10 years.

Although this is an illustrative example, because the scope of the proposed rule would likely include most small entities, FDA uses the example of 100,000 units annualized over 10 years at a 7-percent discount rate to estimate the compliance costs as a proportion of average annual revenue. FDA calculated the average annual value of shipments for each employment category from data from the 2002 Economic Census. Because the agency's analysis of FDA's approval data found that at least one small entity might be required to revise the content of labeling for five innovator products in a single year, tables 10 and 11 of this document show the potential lower and upper bound impact on small manufacturing entities. Even with five affected products in a single year, annualized compliance costs would be less than 1.1 percent of average annual shipments for all establishment sizes.

TABLE 10.—ANNUALIZED COMPLIANCE COSTS AS A PERCENTAGE OF THE VALUE OF AVERAGE ANNUAL SHIPMENTS FOR SMALL PHARMACEUTICAL PREPARATION MANUFACTURING ESTABLISHMENTS (NAICS 325412)

Number of Employees	Number of Establishments	Annual Value of Shipments ($ mil)	Average Per Establishment Annual Value of Shipments ($ mil)	Hypothetical Annualized Costs as a Percentage of Average Annual Value of Shipments[1]	
				1 Affected Product	5 Affected Products
1-19	436	1,101.9	2.5	0.2%	0.8%
20-49	109	978.5	9.0	0.0%	0.2%
50-99	93	2,804.7	30.2	0.0%	0.1%
100-499	184	23,773.2	129.2	0.0%	0.0%
500-999	48	35,262.7	734.6	0.0%	0.0%

Source: Table 4 in Ref. 50.
[1] One time compliance costs annualized at 7 percent for 10 years. Total annualized costs for this example total $3,920 per affected innovator product.

In the year that a small entity revises innovator labeling, the entity might spend up to $13,000 on one-time design costs, one-time printing costs for longer labeling in 8-point type size, and the annual incremental costs of printing longer trade labeling and a PDR listing conforming to the new content requirements. With five affected innovator products in a single year, compliance costs could total up to $65,000. However, FDA approval data suggest that it is unlikely that entities in the smallest category of establishments (i.e., less than 20 employees) would have 5 innovator products requiring revision in a single year. Nevertheless, $65,000 in compliance costs would total less than 4 percent of average annual revenues for an entity with less than 20 employees and less than 1 percent of average annual revenues for small entities with 20 or more employees.

TABLE 11.—ANNUALIZED COMPLIANCE COSTS AS A PERCENTAGE OF THE VALUE OF AVERAGE ANNUAL SHIPMENTS FOR SMALL BIOLOGICAL PRODUCT MANUFACTURING ESTABLISHMENTS (NAICS 325414)

Number of Employees	Number of Establishments	Annual Value of Shipments ($ mil)	Average Per Establishment Annual Value of Shipments ($ mil)	Hypothetical Annualized Costs as a Percentage of Average Annual Value of Shipments[1]	
				1 Affected Product	5 Affected Products
1-19	166	302.4	1.8	0.2%	1.1%
20-49	58	378.5	6.5	0.1%	0.3%
50-99	26	366.5	14.1	0.0%	0.1%
100-499	35	2,719.7	77.7	0.0%	0.0%

Source: Table 4 in Ref. 49.
[1] One time compliance costs annualized at 7 percent for 10 years. Total annualized costs for this example total $3,920 per affected innovator product.

F. Alternatives Considered

1. No New Regulatory Action

This alternative is the baseline against which FDA measures the costs and benefits of the other regulatory alternatives. The current ‘‘Pregnancy,’’ ‘‘Labor and delivery,’’ and ‘‘Nursing mothers’’ subsections of the labeling, including the pregnancy categories, fail to provide relevant clinical information to health care providers and their patients about the safe and effective use of drug

products during pregnancy and lactation. Current labeling also provides no information about the effects of inadvertent exposure before a woman knows she is pregnant.

2. Require the Labeling of Applications Submitted After the Effective Date of the Pregnancy Labeling Final Rule To Conform to the New Content Requirements; Remove the Pregnancy Category From the Labeling of All Other Approved Products (''Prospective Alternative'')

This alternative would require that the new content be added only to the labeling for applications submitted after the effective date of the pregnancy final labeling rule. The scope of this alternative would be narrower than that of the proposed rule. Consequently, FDA estimates that 10 years after the effective date, 1,200 innovator products and 400 generic products would contain the new content. The estimated costs, therefore, would be less than those of the proposed rule. Because the labeling of fewer products would include the new pregnancy labeling content, the potential benefits of this alternative, although uncertain, might be less than those of the proposed rule.

This alternative would also require that, within 3 years of the effective date, manufacturers remove the pregnancy category (if it exists) from all labeling for products approved before the effective date of the pregnancy labeling final rule. FDA's approval data suggests that this requirement would affect about 2,990 innovator products and 3,630 generic products. Like the proposed rule, these changes to labeling would not require a separate labeling supplement, but would be submitted in an annual report.

FDA assumes that most cost components for this alternative are the same as for the proposed rule (see section VIII.C.2 of this document for details). However, because this alternative would only require new content

prospectively, FDA anticipates that no additional agency resources would be needed.

Table 12 of this document shows the estimated costs of this alternative. The estimated one-time costs to add the new content and remove the pregnancy category are $19.2 million. The annual incremental costs to print longer labeling that contains the new content are estimated at $22.3 million. The present value of the total compliance costs of this option would be approximately $29.9 million with a 7-percent discount rate or about $35.8 million with a 3-percent discount rate. The estimated annualized compliance costs for this alternative are $4.2 million with a 3-percent discount rate and $4.3 million with a 7-percent discount rate. Moreover, any overlap of the implementation schedules of the PLR and the pregnancy labeling final rule would reduce these costs because firms could make all labeling changes at the same time. However, any potential cost savings depend on the effective date of the pregnancy labeling final rule.

TABLE 12.—ESTIMATED COSTS OF THE PROSPECTIVE ALTERNATIVE

Year	One-Time Revision Cost ($ mil)	Annual Printing Costs ($ mil)	Total Costs ($ mil)	Present Value ($ mil)	
				3%	7%
1	0.2	0.6	0.8	0.8	0.8
2	0.2	1.2	1.3	1.3	1.2
3	17.6	1.6	19.2	17.6	15.7
4	0.2	1.9	2.1	1.8	1.6
5	0.2	2.1	2.3	2.0	1.7
6	0.2	2.4	2.5	2.1	1.7
7	0.2	2.6	2.8	2.3	1.7
8	0.2	2.9	3.0	2.4	1.8
9	0.2	3.1	3.3	2.5	1.8
10	0.2	3.9	4.1	3.0	2.1
Total	19.2	22.3	41.5	35.8	29.9

3. Require the Labeling of Categories of Drugs That Are Most Widely Used by Pregnant Women and Women of Reproductive Age To Conform to the Content Requirements

The scope of this alternative would be greater than that of the proposed rule. In the agency's efforts to develop this proposed rule, it consulted with outside experts concerning what drugs should be covered by this rule. FDA asked the American College of Obstetrics and Gynecology, the American Academy of Pediatrics, and the Association of Women's Health, Obstetric and Neonatal Nurses were asked about which drugs each thought were important to the clinical care of pregnant women and for which drugs more information is needed. FDA asked the Organization of Teratology Information Services and Motherisk, two organizations that counsel pregnant women about exposure to drugs during pregnancy, to list the drugs about which they received the most questions from pregnant women. FDA also consulted the March of Dimes and the Canadian Pediatric Society. In addition, FDA asked the Pregnancy Labeling Subcommittee of the Advisory Committee for Reproductive Health Drugs to consider how to determine which drugs merited priority implementation of the new content and format for pregnancy labeling. Consultation with these experts resulted in numerous lists of drugs for which revised pregnancy labeling was considered a priority. However, no clear core set of drugs or drug classes emerged from this process. The agency compiled a list of drug classes from those suggested by the various sources. The list included analgesics, anti-infective drugs, anticoagulants, antidepressants, antiemetics, anticonvulsants, antifungals, antihypertensives, antimigraine drugs, antivirals, respiratory agents, thyroid drugs, tranquilizers, oral contraceptives, glucocorticoids, estrogens, gastrointestinal drugs, and antihistamines. Changing the content and

format of pregnancy labeling for such a large universe of drugs would be a large burden for both industry and FDA. Because of the difficulties of identifying the products affected by this alternative, FDA did not estimate the costs of this alternative, but expects that they would fall somewhere between those of the proposed rule and the highest cost alternative described below.

4. Require the Labeling of All Approved Products To Conform to the New Content Requirements

In contrast to the proposed rule, this alternative has the broadest scope and would require that new content be added to the labeling of about 4,170 innovator products and 4,030 generic products. Consequently the estimated costs and potential benefits would be greatest with this alternative.

The implementation schedule and estimated costs for future applications and for approved applications subject to the PLR would be the same as for the proposed rule. Approved applications not subject to the PLR would follow a staggered implementation schedule in which manufacturers would be given from 6 to 10 years to revise product labeling, depending on the approval date. Under this staggered schedule, manufacturers with applications approved before June 30, 1975, would have 6 years to revise labeling; manufacturers with applications approved between June 30, 1975, and June 29, 1984, would have 7 years to revise labeling; manufacturers with applications approved between June 30, 1984, and June 29, 1990, would have 8 years to revise labeling; manufacturers with applications approved between June 30, 1990, and June 29, 1996, would have 9 years to revise labeling; and manufacturers with applications approved between June 30, 1996, to June 29, 2001, would have 10 years to revise labeling.

The length of time since a product's approval determines the amount of information available for the new content. In general, more information about clinical experience is available for older products than for newly approved products. Thus, FDA expects that manufacturers with applications not subject to the PLR might spend more time collecting and organizing the new content and that the costs to print longer labeling may exceed those estimated for applications subject to the PLR. Because the new content for older products could be longer than that for newly approved products, additional FDA personnel might be needed to review the labeling supplements for older products.

To account for these potential differences in the costs for the labeling of older products, this analysis uses a range of costs for products not subject to the PLR. One-time costs to collect and organize information range from $3,000 to $6,000 for innovator products. The length of trade labeling might increase by 12-square inches at a cost of $750 for innovator products and $450 for generic products. If the labeling of older products is longer than that of newly approved products, manufacturers with older innovator products might incur costs for labeling distributed directly to consumers and health care providers and costs to print longer labeling in the PDR. For this alternative, FDA estimates that, on average, labeling printed in 8-point type size would increase by 38 square inches at a cost of $8,050, and the PDR would be about 0.3 page longer at a cost of $3,950. Finally, to account for a potential increase in FDA resources for this alternative, the number of additional FTEs would double from two to four for the last 5 years of the analysis.

Over 10 years, the one-time costs to revise labeling to add the new content could range from $29.2 million to $34.3 million. Annual incremental printing

costs might total about $91.5 million over 10 years. The present value of the total compliance costs range from about $75.3 million to about $78.2 million with a 7-percent discount rate and from about 97.9 million to about $101.9 million with a 3-percent discount rate. The estimated annualized compliance costs for this alternative, therefore, range from $11.5 million to $11.9 million with a 3-percent discount rate and range from $10.7 million to $11.1 million with a 7-percent discount rate. Table 13 shows the upper bound estimate for this alternative.

TABLE 13.—UPPER BOUND ESTIMATED COSTS OF HIGHEST IMPACT ALTERNATIVE

Year	Number of Approved Applications by Type of Product		Total Costs ($ mil)	Present Value ($ mil)	
	Innovator	Generic		3%	7%
1	140	40	1.3	1.2	1.2
2	130	40	1.8	1.7	1.5
3	500	300	6.7	6.1	5.5
4	600	170	9.3	8.3	7.1
5	560	250	11.2	9.7	8.0
6	480	630	15.5	13.0	10.3
7	430	720	16.7	13.6	10.4
8	390	650	17.7	13.9	10.3
9	450	670	20.0	15.3	10.9
10	490	560	25.6	19.1	13.0
Total	4,170	4,030	125.8	101.9	78.2

5. Summary of Regulatory Options

Table 14 of this document shows the total and incremental costs of the proposed rule and regulatory alternatives. The total benefits of the regulatory alternatives would be directly related to the costs, because the more costly the alternative the more products that would be covered. It should be noted that although the total benefits would correspond to the total costs, the marginal benefits of these alternatives may not correspond directly to marginal costs. FDA is unable, however, to quantify the total or incremental benefits of these regulatory alternatives.

The requirements of this proposed rule are the result of the agency's efforts to revise the regulations concerning the content and format of the ''Pregnancy,'' ''Labor and delivery,'' and ''Nursing mothers'' subsections of prescription drug labeling. Although the prospective alternative has lower costs than the proposed rule, it would result in two types of PLR labeling—one with the revised pregnancy and lactation content and one without the revised content. To ensure the consistent quality of labeling subject to the PLR, the agency, therefore, proposes that the pregnancy labeling rule apply to all labeling subject to the PLR.

TABLE 14.—COMPARISON OF THE ESTIMATED COMPLIANCE COSTS OF THE PROPOSED RULE AND THE REGULATORY ALTERNATIVES[1]

Alternatives	Annualized costs ($ million)		Incremental costs ($ million)	
	3 percent	7 percent	3 percent	7 percent
No new regulatory action	0	0	N/A	N/A
Content required for labeling prospectively	4.2	4.3	4.2	4.3
Proposed rule	7.7	7.6	3.5	3.3
Content required for labeling of most widely used drugs	7.7 < x < 11.9	7.6 < x < 11.1	0 < x < 4.2	0 < x < 3.5
Content required for labeling of all approved drugs	11.5 to 11.9	10.7 to 11.1	3.8 to 4.2	3.1 to 3.5

[1] The present value of the total estimated compliance costs are annualized over 10 years at a 3–percent discount rate or a 7–percent discount rate. Compliance costs include the costs to remove the pregnancy categories from labeling not subject to the content requirements of each alternative.

IX. Paperwork Reduction Act of 1995

This proposed 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). A description of these requirements is given below, along with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity

of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

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

Description: The proposed rule would amend FDA regulations concerning the format and content 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 proposal would require that labeling include a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. The labeling would also include relevant clinical information to help health care professionals make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The proposal would eliminate the current pregnancy categories A, B, C, D, and X. The ''Labor and delivery'' subsection would be eliminated because information on labor and delivery would be included in the ''Pregnancy'' subsection. The proposed rule is intended to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that will be useful for decisionmaking by women of childbearing age and their health care providers.

Under proposed §§ 201.57(c)(9)(i) and 201.57(c)(9)(ii), holders of approved applications[7] would be required to provide new labeling content in a new format—that is, to completely rewrite the pregnancy and lactation portions of

[7] As discussed previously, the term ''application'' refers to NDAs, BLAs, and efficacy supplements.

each drug's labeling. These application holders would be 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 proposed § 201.80(f)(6)(i), holders of approved applications would be 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 would 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 proposed rule would apply to all applications that are required to comply with the PLR, including: (1) Applications submitted on or after the date the proposed rule becomes final; (2) applications pending on the date the proposed rule becomes final; and (3) applications approved from June 30, 2001, to the effective date of the pregnancy labeling rule.

Information collection subject to the PRA would consist of the following submissions under the proposed rule:

(1) Applications submitted on or after the effective date of the proposed rule (§§ 314.50; 314.70(b); 601.2; 601.12(f)(1));

(2) Amendments to applications pending on the effective date of the final rule (§ 314.60);

(3) Supplements to applications approved from June 30, 2001, to the effective date of the final rule (§ 314.70(b); 601.12(f)(1));

(4) Holders of applications approved before June 29, 2001, that contain a pregnancy category would be required to remove the pregnancy category designation by 3 years after the effective date of the final rule and include this labeling change in their annual report (§ 314.70(d), 601.12(f)(3)).

The information collection requirements and burden estimates are summarized in table 12 of this document. Based on data provided in section VIII of this document, FDA estimates that approximately 1,613[8] applications containing labeling consistent with this rulemaking would be submitted to FDA by approximately 885 applicants. Based on data provided in section VIII of this document, FDA estimates that it would take applicants approximately 20 hours to prepare and submit labeling consistent with this rulemaking. The estimate of 20 hours is incremental, in that it applies only to the requirements for 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 Number 0910–0572.

FDA also estimates that approximately 111 amendments to applications pending on the effective date of the pregnancy labeling final rule would be submitted to FDA as a result of this proposal, by approximately 81 applicants, and that it would take those applicants approximately 20 hours (incremental) to prepare and submit each amendment.

In addition, FDA estimates that approximately 1,789 supplements to approved applications would be submitted to FDA to update labeling in accordance with this proposal, that approximately 210 application holders would submit these supplements, and that it would take those application holders approximately 85 hours[9] (incremental) to prepare and submit each supplement.

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[8] 1,613 includes approximately 1,197 innovator and 416 generic drug products.

[9] The estimate for innovator companies is approximately 85 hours, and the estimate for generic companies is approximately 22 hours. For purposes of this information collection analysis, FDA used the higher estimate and invites comment on the time needed to prepare and submit these supplements.

FDA also estimates that approximately 4,720[10] annual reports containing labeling changes resulting from this rulemaking would be submitted to FDA by approximately 300 application holders, and that it would take application holders approximately 50 hours[11] to prepare and submit each revision.

FDA must request an extension of approval of this information collection every 3 years. For purposes of OMB approval for the first 3-year period, FDA divided the total hours in table 15 of this document (422,545 hours) by 3 to provide OMB an annualized estimate of burdens associated with this rulemaking (i.e., 140,848 hours).

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

Burden Estimate: Table 15 of this document provides an estimate of the annual reporting burden for the proposed pregnancy and lactation labeling requirements. FDA specifically requests comments on these estimates.

TABLE 15.—ESTIMATED ANNUAL REPORTING BURDEN[1]

Category (21 CFR section)	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
New NDAs/ANDAs/BLAs/efficacy supplements submitted on or after effective date (§§ 314.50; 314.70(b); 601.2; 601.12(f)(1))	885	1.82	1,613	20	32,260
Amendments to applications pending on effective date (§ 314.60)	81	1.37	111	20	2,220
Supplements to applications approved 6/30/01 to effective date (§ 314.70(b); 601.12(f)(1))	210	8.52	1,789	85	152,065
Annual report submission of revised labeling for applications approved before 6/29/01 that contain a pregnancy category (§ 314.70(d); 601.12(f)(3))	300	15.73	4,720	50	236,000
Total					422,545

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

In compliance with section 3507(d) of the PRA, the agency has submitted the information collection requirements of this proposed rule to OMB for

[10] 4,720 includes approximately 1,697 innovator and 3,023 generic drug products.

[11] The estimate for innovator companies is approximately 50 hours, and the estimate for generic companies is approximately 22 hours. For purposes of this information collection analysis, FDA used the higher estimate and invites comment on the time needed to prepare and submit these supplements.

review. The information collection provisions of this proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding information collection by [*insert date 30 days after date of publication in the* **Federal Register**], to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–6974, or e-mailed to: *baguilar@omb.eop.gov.*

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' In this proposed rule, FDA is proposing to revise its existing requirements concerning the format and content of the ''Pregnancy,'' ''Labor and delivery,'' and ''Nursing mothers'' subsections of labeling for human prescription drug and biological products. To the extent that a State requires labeling that conflicts with these requirements, the State required labeling would be subject to implied conflict preemption.

As stated in the preamble, this proposed rule would amend portions of FDA's regulations that were recently revised by the PLR. When FDA finalized the PLR, the agency responded to comments regarding the product liability implications of revising the labeling for prescription drugs. Several comments on the proposed PLR had raised concerns about State requirements on drug

labeling, often as a result of product liability lawsuits, that conflict with federal requirements. As a result of those comments, and in discussing federalism issues, FDA restated its longstanding views on preemption. For further discussion of this issue, see 71 FR 3922 at 3933 through 3936 and 3967 through 3969. FDA's statements in this regard are applicable to this proposed rule as well, and reflect the agency's current position on this issue. Section 4(c) of Executive Order 13132 instructs us to restrict any Federal preemption of State law to the ''minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated.'' This proposed rule meets the preceding requirement because as discussed above, it would preempt State laws that conflict with these Federal requirements. Section 4(d) of Executive Order 13132 states that when an agency foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility, the agency ''shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict.'' In this case, FDA foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility. Section 4(e) of Executive Order 13132 adds that ''when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency ''shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.''

FDA is seeking input from all stakeholders on the proposed requirements for the content and format of pregnancy labeling through publication of the proposed rule in the **Federal Register** and will consult with State and local officials in an effort to avoid conflict between State law and federal protected interests.

XI. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Please note that on January 15, 2008, the FDA Division of Dockets Management Web site transitioned to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. Electronic comments or submissions will be accepted by FDA only through FDMS at *http://www.regulations.gov*.

XII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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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, it is proposed that 21 CFR part 201 be 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 place the subheading ''8.2 Lactation''.

3. Section 201.57 is amended by removing and reserving paragraph (c)(9)(iii) and by revising paragraphs (c)(9)(i) and (c)(9)(ii) 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:

(A) *Pregnancy exposure registry*. 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 stated at the beginning of the ''Pregnancy'' subsection of the labeling.

(B) *General statement about background risk*. The following statement must be included:

''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.''

(C) *Fetal risk summary*. Under the subheading ''Fetal Risk Summary,'' the labeling must contain 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.

(*1*) Using the risk conclusions provided in paragraphs (c)(9)(i)(C)(*2*) and (c)(9)(i)(C)(*3*) of this section, 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). More than one risk conclusion may be needed to characterize the likelihood of risk for different developmental abnormalities, doses, durations of exposure, or gestational ages at exposure. 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. The source(s) of the data that are the basis for the fetal risk summary must be stated. If data demonstrate that a drug is not systemically absorbed, the fetal risk summary must contain only the following statement, without any other risk conclusion:

''(*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.''

(*2*) *Risk conclusions based on human data*. When both human and animal data are available, risk conclusions based on human data must be presented before risk conclusions based on animal data. A risk conclusion based on

human data must be followed by a narrative description of the risks as described in paragraph (c)(9)(i)(C)(*4*) of this section.

(*i*) *Risk conclusions based on sufficient human data*. Sufficient human data may come from such sources as clinical trials, pregnancy exposure registries or other large scale epidemiologic studies, or case series reporting a rare event. 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*).''

(*ii*) *Risk conclusions based on other human data*. When human data are available but are not sufficient to use one of the risk conclusions listed in paragraph (c)(9)(i)(C)(*2*)(*i*) of this section, the likelihood that the drug increases the risk of developmental abnormalities must be characterized as low, moderate, or high.

(*3*) *Risk conclusions based on animal data*. 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:

(*i*) *Not predicted to increase the risk*. When animal data contain no findings for any developmental abnormality, the fetal risk summary must state: ''Based on animal data, (*name of drug*) is not predicted to increase the risk of developmental abnormalities (see Data).''

(*ii*) *Low likelihood of increased risk*. When animal data contain findings of developmental abnormality but the weight of the evidence indicates that the findings are not relevant to humans (e.g., findings in a single animal species that are caused by unique drug metabolism or a mechanism of action thought not to be relevant to humans; findings at high exposures compared with the maximum recommended human exposure), the fetal risk summary must state: ''Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be low (see Data).''

(*iii*) *Moderate likelihood of increased risk*. When animal data contain findings of one or more fetal developmental abnormalities in one or more animal species, and those findings are thought to be relevant to humans, the fetal risk summary must state: ''Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be moderate (see Data).''

(*iv*) *High likelihood of increased risk*. When animal data contain robust findings of developmental abnormalities (e.g., multiple findings in multiple animal species, similar findings across species, findings at low exposures compared with the anticipated human exposure) thought to be relevant for humans, the fetal risk summary must state: ''Based on animal data, the likelihood that (*name of drug*) increases the risk of developmental abnormalities is predicted to be high (see Data).''

(*v*) *Insufficient data*. When there are insufficient animal data or no animal data on which to assess the drug's potential to increase the risk of developmental abnormalities, the fetal risk summary must so state (see Data).

(*4*) *Narrative description of risk(s)*. 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.

(*5*) *Contraindications, warnings, and precautions*. If there is information in the ''Contraindications'' or ''Warnings and Precautions'' section of the labeling on an increased risk to the fetus from exposure to the drug, the fetal risk summary must refer to the relevant section.

(D) *Clinical considerations*. Under the subheading ''Clinical Considerations,'' the ''Pregnancy'' subsection of the labeling must provide the following information:

(*1*) *Inadvertent exposure during pregnancy*. 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.

(*2*) *Prescribing decisions for pregnant women*. The labeling must provide the following information:

(*i*) The labeling must describe the risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat.

(*ii*) *Information about dosing adjustments during pregnancy must be provided*. This information must also be included in the ''Dosage and Administration'' and ''Clinical Pharmacology'' sections of the labeling. If there are no data on dosing in pregnancy, the labeling must so state.

(*iii*) If use of the drug is associated with maternal adverse reactions that are unique to pregnancy or if known adverse reactions occur with increased frequency or severity in pregnant women, the labeling must describe the adverse reactions. 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(s). The labeling must describe any interventions that may be needed (e.g., monitoring blood glucose for a drug that causes hyperglycemia in pregnancy).

(*iv*) If it is known or anticipated that treatment of the pregnant woman will cause a complication in the neonate, the labeling must describe the complication, the severity and reversibility of the complication, and general types of interventions, if any, that may be needed.

(*3*) *Drug effects during labor or delivery*. If 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, the labeling must provide the 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.

(E) *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.

(ii) *8.2 Lactation*. This subsection of the labeling must contain the following information in the following order:

(A) *Risk summary*. Under the subheading ''Risk Summary,'' if, as described under § 201.57(c)(9)(ii)(A)(*1*) through (c)(9)(ii)(A)(*3*) of this 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 breast-feeding.'' 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. 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 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 breast milk. Breast-feeding is not expected to result in fetal exposure to the drug.'' If the drug is absorbed systemically, the risk summary must describe the following to the extent information is available:

(*1*) *Effects of drug on milk production*. 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.

(*2*) *Presence of drug in human milk*.

(*i*) 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.

(*ii*) If studies demonstrate that the drug is not detectable in human milk, the risk summary must state the limits of the assay used.

(*iii*) 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 percent of the maternal dose excreted in human milk.

(*3*) *Effects of drug on the breast-fed child*. The risk summary must contain information on the likelihood and seriousness of known or predicted effects on the breast-fed child from exposure to the drug in human milk. The risk summary must be 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.

(B) *Clinical considerations*. 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 breast-feeding 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.

(*3*) Information about dosing adjustments during lactation. This information must also be included in the ''Dosage and Administration'' and ''Clinical Pharmacology'' sections.

(C) *Data*. 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.

* * * * *

§ 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*).

[This appendix will not appear in the Code of Federal Regulations.]

APPENDIX

This appendix contains examples of how to apply the proposed rule depending on the type of data available. All examples use hypothetical drugs.

SAMPLE PREGNANCY SUBSECTION LABELING

1. Drug for which only animal data are available; with developmental toxicity findings:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes ALPHATHON's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Based on animal data, the likelihood that ALPHATHON increases the risk of developmental abnormalities is predicted to be high (see Data).

Clinical Considerations

Asthma complicates approximately 1 percent of all pregnancies resulting in higher perinatal mortality, low birth weight infants, preterm births, and pregnancy-induced hypertension compared to outcomes for nonasthmatic women. Because of the risks of even mild maternal hypoxia to the developing fetus, asthma should be clinically well-controlled during pregnancy. There are no human studies evaluating ALPHATHON use in pregnant women. The time of gestation at which risk may be greatest is unknown; therefore, risks of inadvertent exposure in early gestation cannot be evaluated. Animal data suggest that ALPHATHON exposure may result in early fetal loss and anomalies of major organ systems. There are no data regarding dose adjustment needs in pregnancy. Given the lack of human data and the risks suggested by animal data, prescribers should consider alternative treatments for asthma for pregnant women when possible (especially during the first trimester) and women planning pregnancy.

Data

Human data.

- There are no data on human pregnancies exposed to ALPHATHON.

Animal Data.

- Reproductive studies performed during early pregnancy in rats at oral doses 0.75 to 1.0 times the recommended human dose (adjusted for body surface area) showed implantation loss, fetal resorptions, and major congenital anomalies of the cardiac, skeletal and renal systems without signs of maternal toxicity.
- Reproductive studies performed in early pregnancy in rabbits at doses approximately 0.33 to 1.0 times the recommended human dose (adjusted for body surface area) showed increased post-implantation loss. Studies at 3 times the human dose showed significant fetal loss without signs of maternal toxicity.
- The effects of ALPHATHON on fetal growth, labor, or post-natal complications were not evaluated in the animal studies.

2. Drug for which only animal data are available; lack of developmental toxicity findings:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes GAMMAZINE's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Based on animal data, GAMMAZINE is not predicted to increase the risk of developmental abnormalities.

Clinical Considerations

Infection of the urinary tract in pregnant women carries a higher risk of morbidity than in the general population and is associated with an increased incidence of preterm delivery, low birth weight, and progression to

pyelonephritis. It is not known whether the dose of GAMMAZINE requires adjustment during pregnancy.

Data

Human Data.

- There are no data on human pregnancies exposed to GAMMAZINE.

Animal Data.

- No teratogenic effects were seen when pregnant rats and rabbits were treated throughout pregnancy with doses equivalent to 1.5 times the maximum recommended human dose adjusted for body surface area. There were no findings of increased fetal loss, mortality or resorptions, reductions in body weights in fetuses, or other developmental abnormalities.

3. Drug for which animal and some human (insufficient) data are available:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes KAPPAATE's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Based on limited human data from one retrospective cohort study and postmarketing adverse event reporting, the likelihood that KAPPAATE increases the risk of major congenital abnormalities or spontaneous abortions is low. Short term (less than 3 weeks), first trimester exposure to 5 to 10 milligrams per (mg/) day of KAPPAATE did not result in an increase in major congenital abnormalities or spontaneous abortions over the background rate. The limited number of pregnant women that were exposed to KAPPAATE during the second and third trimesters delivered infants with no major congenital abnormalities. Based on animal data, the likelihood that

KAPPAATE increases the risk of developmental abnormalities is predicted to be moderate.

Clinical Considerations

Symptoms of heartburn and gastroesophageal reflux disease (GERD) are common during pregnancy, occurring in about 50 percent of women in the third trimester. During pregnancy, untreated GERD can lead to reflux esophagitis and can increase nausea and asthma exacerbations in asthmatics. Based on limited human data, inadvertent exposure to KAPPAATE in early pregnancy is unlikely to be associated with major congenital abnormalities or spontaneous abortions; however, animal data suggest that early fetal loss may result from KAPPAATE exposure. Pharmacokinetic studies have shown that no dose adjustment of KAPPAATE is needed for pregnant women in the third trimester (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY). Pharmacologically similar drugs have demonstrated delayed parturition in animal studies, but the relevance of this finding in humans is not known.

Data

Human Data.

- A retrospective cohort study reported on 400 pregnant women who used 5 to 10 mg/day of KAPPAATE in the first trimester.[1] The majority of use (90 percent) was short term (less than 3 weeks). The overall malformation rate for first trimester exposure to KAPPAATE was 3.4 percent (95 percent CI 1.3-7.2) compared to 4.1 percent (95 percent CI 1.6-6.2) in the comparator group. The study could effectively rule out a relative risk greater than 2.0 for overall

[1] Smith J.D., M.R. Perkins, ‘‘Retrospective study on pregnant women exposed to Kappaate,’’ *Some Medical Journal*, 121(55):123–134, 2002.

malformations. Rates of spontaneous abortions did not differ between the groups.

- Postmarketing reports on 125 women exposed to 5 to 10 mg/day of KAPPAATE during pregnancy did not suggest an increased risk of major congenital malformations compared to the background rate in the general population. However, gestational ages and durations of exposure were not available for all cases. Interpretation of these results are limited by the voluntary nature of postmarketing adverse event reporting and underreporting.
- No change in pharmacokinetics were seen in pregnant women at 32 to 36 weeks gestation given a single dose of KAPPAATE (see CLINICAL PHARMACOLOGY).

Animal Data.

- In rats, no teratogenic or embryocidal effects were observed when KAPPAATE was administered at doses up to 7 times the human dose on a body surface area basis).
- In rabbits, KAPPAATE at maternal doses about 5 to 50 times the human dose on a body surface area basis produced dose-related increases in embryo-lethality, fetal resorptions, pregnancy disruptions, and fetal growth impairment.
- No effects were seen on parturition.

4. Drug for which sufficient human data are available:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Deltaman's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Human data do not indicate that DELTAMAN increases the overall risk of congenital malformations or neural tube defects. The majority of reported human exposures to DELTAMAN are first trimester exposures. Epidemiology studies adequate to detect a 2.5-fold increase in the rate of major malformations and a 10-fold increase in the rate of neural tube defects did not detect a risk. Based on animal data, the likelihood that DELTAMAN increases the risk of other developmental abnormalities is predicted to be low.

Clinical Considerations

About 1 in 100 women of childbearing age has diabetes. During pregnancy, diabetic women have increased risks of miscarriage, preterm labor, stillbirth, macrosomia, and congenital malformations, including heart defects and neural tube defects. Neonates born to women with poorly controlled diabetes are at increased risk of breathing difficulties, low blood sugar levels and jaundice. Based on human data, inadvertent exposure to DELTAMAN in early pregnancy is not associated with an increased risk of major congenital abnormalities or neural tube defects. There are no data regarding whether dosing adjustments are needed when DELTAMAN is used in pregnancy.

Data

Human Data.

- The DELTAMAN Pregnancy Exposure Registry, a population-based prospective cohort epidemiological study, has collected data since January 2000. As of December 2007, the registry documented outcomes on 1,055 infants exposed to DELTAMAN during pregnancy (997 exposed during the first trimester and 58 exposed after the first trimester) have been documented. In utero exposure to DELTAMAN was not associated with an increased risk of major congenital malformations at birth (odds ratio 0.93, 95 percent CI 0.52-

1.39). The number of infants born with neural tube defects was similar in the DELTAMAN exposed infants and controls. The sample size in this study had 90 percent power to detect a 2.5-fold increase in the rate of major malformation and 80 percent power to detect a 10-fold increase in the rate of neural tube defects.

- A retrospective cohort study reported on 869 pregnant women exposed to either DELTAMAN or pharmacologically similar drugs in the first trimester (245 exposed to DELTAMAN).[2] The overall major malformation rate was 4.1 percent (95 percent CI 3.2-5.1) and the malformation rate for first trimester exposure to DELTAMAN was 3.4 percent (95 percent CI 1.3-7.8). The relative risk of major malformations associated with first trimester exposure to DELTAMAN compared with nonexposed women was 0.92 (95 percent CI 0.34-2.3). The sample size in this study had 80 percent power to detect a 4-fold increase in the rate of major malformations.

Animal Data.

- Exposure of pregnant rats or mice to DELTAMAN at doses comparable to the maximum recommended human dose (based on body surface area) resulted in embryonic death and malformations in the offspring. Skeletal abnormalities were the most common malformations observed in rats and cardiac, skeletal and urinary tract abnormalities were seen most often in mice. Neural tube defects were observed in pregnant mice and rats at doses of 15 to 25 and 5 to 20 times the human dose (based on body surface area), respectively. Behavioral alterations and poor weight gain were seen among the offspring of rats treated with DELTAMAN during pregnancy at doses greater than 15 times the maximum human dose (based on body surface area).

[2] Jones A.B. and C.D. Smith, ‘‘Exposure to Deltaman during pregnancy,’’ *Medical Journal*, 98:56–68, 2000.

- Studies in cynomolgus monkeys at 1 to 10 times the maximum recommended human dose (based on a body surface area) demonstrated a dose dependent increase in neural tube and skeletal anomalies.

SAMPLE LACTATION SUBSECTION LABELING

1. Drug for which no data are available:

Risk Summary

No studies have been conducted to assess ALPHAZINE's impact on milk production, its presence in breast milk or its effects on the breast-fed child.

Clinical Considerations

Other medical therapies are available for the treatment of maternal hypertension.

Data

No data available.

2. Drug for which pharmacologic class information is available, but no human data are available:

Risk Summary

No studies have been conducted to assess THETAM's effect on milk production, its presence in breast milk, or its effects on the breast-fed child. Based on experience with other products in this class, maternal THETAM use has the potential to cause neutropenia in the breast-fed child. Because of the potential for neutropenia in the breast-fed child, a decision should be made whether to discontinue breast-feeding or discontinue using THETAM.

Clinical Considerations

Other medical therapies are available for the treatment of maternal fungal infection.

Data

No data available.

3. Drug for which human data are available:

Risk Summary

GAMMATOL is secreted in human milk. At a maternal dose of 400 mg daily, the average milk concentration, collected over 24 hours after dosing, was 10 mcg/milliliter (mL) which is lower than maternal serum drug concentrations at steady state. Based on an average milk consumption of 150 mL/kilogram (kg)/day, a 2-month-old infant would consume approximately 6 mg/day of GAMMATOL via breast milk, which is approximately 1.3 percent of the maternal dose. No studies have been performed to assess infant absorption and exposure to GAMMATOL from breast milk. No studies have been performed to assess the impact of GAMMATOL on milk production or its effects on the breast-fed child.

Clinical Considerations

Because GAMMATOL is taken once daily, mothers can reduce infant exposure by taking their GAMMATOL dose immediately after breast-feeding at the time of day when feedings are less frequent.

Data

- A lactation study was performed in 30 women who were 2 months postpartum and exclusively breast-feeding their infants. All women enrolled in the study were taking a 400 mg single dose of GAMMATOL daily. Breast milk samples were collected from each breast at the beginning and end of each feeding for 24 hours after a GAMMATOL dose. An average maximum milk concentration of 20 mcg/mL occurred 3 hours after dosing and drug concentrations in milk rapidly declined over the next 12 hours. The average milk concentration was 10 mcg/mL. No drug was detectable in milk samples

obtained 36 hours or later after dosing. No data are available to assess the impact of GAMMATOL on milk production or its effects on the breast-fed child.

Dated: May 16, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. 08–????? Filed ??–??–08; 8:45 am]

BILLING CODE 4160–01–S