表9.-3つの生産レベルでの、単一の新薬を製造している仮想的な小企業にかかる推定コスト1

コストカテゴリー	1年間の製造販売単位		
	100,000	10,000	1,000
1回コスト：2			
既存のtrade 添付文書に新たな内容を追加 処方薬に付随しない添付文書を作成 1回コストの総数			
年間コスト増分：			
文字数の多いtrade 添付文書の印刷3 より長いPDRの掲載4 年間コスト増分の合計			
1年間あたりのコスト			
割引率3%での合計年間コスト 割引率3%での販売1単位あたりの追加年間コスト 割引率7%での合計年間コスト 割引率7%での販売1単位あたりの追加年間コスト			

1　丸め誤差があるため、コストが合計と一致しないことがある。

2　1回コストには、新規内容の情報収集とまとめ($1,500)。trade 添付文書の改定 ($2,920；本文書表6の中規模企業を参照)、8ポイントの文字で添付文書のアートワークを作成($1,000)、医療プロバイダーに直接配布するため8ポイントの文字添付文書を印刷するコストが含まれている。

3　印刷するtrade 添付文書の部数は、年間生産単位数に10%の消耗因子を加え、1部あたりの印刷コストの増分$0.0005で計算する。

4　年間10,000単位未満の製品は、PDRに添付文書を掲載しないと仮定。

5　1回コストを10年間に割り振っている。

表10.-小規模製薬業(NAICS 325412)の平均年間出荷額あたりのパーセンテージで示した年あたりのコンプライアンスコスト

従業員数	企業数	年間出荷額（100万ドル）	企業あたりの年間出荷額の平均（100万ドル）	年間出荷額あたりの割合としての仮想的な年間コスト1	
				影響を受ける製品が1つ	影響を受ける製品が5つ

出典：文献50の表4

1　1回コンプライアンスは、割引率7%として10年間に割り振ったもの。この例での年間合計コストは、影響を受ける新薬1種類あたり$3,920

表11.-小規模生物製剤企業(NAICS 325414)の平均年間出荷額あたりのパーセンテージで示した年あたりのコンプライアンスコスト

従業員数	企業数	年間出荷額（100万ドル）	企業あたりの年間出荷額の平均（100万ドル）	年間出荷額あたりの割合としての仮想的な年間コスト1	
				影響を受ける製品が1つ	影響を受ける製品が5つ

出典：文献49の表4

1　1回コンプライアンスは、割引率7%として10年間に割り振ったもの。この例での年間合計コストは、影響を受ける新薬1種類あたり$3,920

表12.-前向き代替案での推定コスト

年	1回改定コスト（100万ドル）	年間印刷コスト(100万ドル)	合計コスト（100万ドル）	現在価値（百万ドル）	
				3%	7%

表13.-影響が最も大きい代替案での推定コストの上限

年	タイプ別の承認済み申請の数		合計コスト（100万ドル）	現在価値（100万ドル）	
	新薬	ジェネリック		3%	7%

表14.-改定案と代替案の推定コンプライアンスコストの比較

代替案	年間コスト（百万ドル）		コスト増分（百万ドル）	
	3%	7%	3%	7%
規則を改定しない				
新たに承認を受ける医薬品の添付文書に内容改定が必要				
この改定案				
最も広く使われている添付文書の内容改定が必要				
全ての承認約の添付文書の内容改定が必要				

1　合計コンプライアンスコストの推定値の現在価値を3%の割引率、あるいは7%の割引率で、10年間にわたって割り振ったもの。コンプライアンスコストにいは、それぞれの代替案で内容改定の要件を満たさない添付文書から妊娠カテゴリーを削除するコストが含まれている。

表15.-報告に要する推定年間負荷1

カテゴリー(21 CFRセクション)	報告者の数	報告者あたりの報告件数	全報告	準備に要する時間	合計時間
発効日以降に提出される新たなNDAs/ANDAs/BLAs/有効性補完サプリメント(§§ 314.50; 314.70(b); 601.2; 601.12(f)(1))					
発効日に保留となっていた申請の修正(§314.60)					
2001年6月30日から発効日までの間に承認された申請のサプリメント(§ 314.70(b); 601.12(f)(1))					
妊娠カテゴリーを含んでいる2001年6月29日より前に承認された申請の添付文書を改定したことの年次報告の提出(§ 314.70(d); 601.12(f)(3))					
合計					

1この情報収集に伴う資本コストや運転、保守コストはない。

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, CLASS B, CLASS C, CLASS D, AND CLASS E AIRSPACE AREAS; AIRWAYS; ROUTES; AND REPORTING POINTS

1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§71.1 [Amended]

2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9R, *Airspace Designations and Reporting Points,* signed August 15, 2007, and effective September 15, 2007, is to be amended as follows:

* * * * *

Paragraph 6005 Class E Airspace Extending Upward From 700 Feet or More Above the Surface of the Earth.

* * * * *

AAL AK E5 Red Dog, AK [Revised]

Red Dog Airport, AK
(Lat. 68°01'56" N., long. 162°54'14" W.)

That airspace extending upward from 700 feet above the surface within an 11-mile radius of the Red Dog Airport, AK, and 4 miles either side of the 219°(T)/238°(M) bearing from the Red Dog Airport, AK, extending from the 11-mile radius to 14.5 miles southwest of the Red Dog Airport, AK; and that airspace extending upward from 1,200 ft. above the surface within a 72.5-mile radius of the Red Dog Airport, AK.

* * * * *

Issued in Anchorage, AK, on May 16, 2008.

Anthony M. Wylie,

Manager, Alaska Flight Services Information Area Group.

[FR Doc. E8–11971 Filed 5–28–08; 8:45 am]

BILLING CODE 4910–13–P

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 August 27, 2008. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by June 30, 2008, (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.

FOR FURTHER INFORMATION CONTACT:

Christine F. Rogers, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041, or

Stephen Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N Rockville, MD 20856, 301–827–6210.

SUPPLEMENTARY INFORMATION:

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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 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

[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.

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 (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.

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

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