FDA's Proposed Rule for Pregnancy and Lactation Labeling: Improving Maternal Child Health Through Well-informed Medicine Use

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ABSTRACT

For the US Food and Drug Administration (FDA), the May 29, 2008 publication of the Proposed Rule for Pregnancy and Lactation Labeling for Human Prescription Drug and Biological Products heralded both an end and a beginning. It marked an end to the labeling initiative process that produced the Proposed Rule and the beginning of FDA's second-generation approach to labeling drugs and biologics for use during pregnancy, breastfeeding, and the childbearing years. These proposed changes reflect the extensive input and feedback FDA collected from clinicians and experts, and are designed to facilitate informed counseling about and prescribing of medicines for women who are pregnant, breastfeeding, or of childbearing potential.

The prescription drug label is FDA's communication tool—it is the place to clearly convey what is known about the safe and effective use of a drug in various populations. With development and implementation of the Physician Labeling Rule (PLR), FDA transformed the prescription drug label into a better communication tool in which information is better organized, clearly presented, and more easily located. The Proposed Rule for Pregnancy and Lactation Labeling is the final piece of PLR, creating a detailed and defined framework in which to present what is and is not known about the use of drugs during pregnancy and breastfeeding.

MEDICINE USE AND PREGNANCY IN THE UNITED STATES

There are more than 60 million women in the United States between the ages of 15 and 44 years. Each year, 1 of 10 women of childbearing potential gets pregnant [1], and 50% of these pregnancies are unplanned [2]. Like women who are not pregnant, some pregnant women need to use drugs and biological therapeutic products to manage chronic disease conditions or treat acute medical problems that coincidently arise during pregnancy or are caused by pregnancy. Data suggest that women receive an average of 3 to 5 drug prescriptions during each pregnancy and that 64% of pregnant women use at least 1 prescription drug. [3]

Assessing the risks and benefits of drug treatment options during pregnancy is a complex and highly individualized process. Optimizing the mother's health can indirectly benefit the embryo or fetus by improving the uterine/placental environment in which the embryo/fetus grows. Sometimes, not treating the mothers' condition during pregnancy can adversely affect the fetus as well as the mother. For example, if a mother has a severe asthma attack or a prolonged seizure, the fetus may suffer an injury due to hypoxia. If a mother has untreated hypertension, she is more likely to deliver a growth restricted infant or experience placental abruption with the associated risks of preterm delivery, fetal hypoxia, and possible fetal death. So, in pregnancy, drug treatment offers direct benefits to the mother and indirect benefits to the embryo/fetus as well as potential risk.

FDA'S FIRST-GENERATION REGULATIONS FOR PREGNANCY AND LACTATION LABELING

FDA first published specific requirements for pregnancy, labor and delivery, and nursing mothers labeling in 1979 (21 CFR

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Table 1: FDA Pregnancy Categories (language summarized from 21CFR201.57)

Category	Definition
A	Adequate and well-controlled (AWC) 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).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, *or* animal studies demonstrate a risk and AWC studies in pregnant women have not been done during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, *and* the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. *Or* animal studies have not been conducted and there are no AWC studies in humans.
D	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 (e.g., if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities *or* 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 (e.g., safer drugs or other forms of therapy are available).

201.57) (44 FR 37434 June 26, 1979). These regulations were developed in response to the 1962 thalidomide disaster, when thousands of babies were born in Western Europe with severe limb deformities. In Europe, thalidomide was marketed as a sleeping pill and was used widely by women of reproductive age. A FDA medical officer, Dr. Frances Kelsey, helped prevent the approval and marketing of thalidomide in the United States. The 1979 regulations established the 5 pregnancy categories (*Table 1*). Each category was defined by the presence or absence of data, the source of the data (animal and/or human) and the results of the studies (positive findings or negative). Some categories (D and X) also included consideration of the drug's benefits to the mother as well as the potential risks to the fetus. Based on the category, the regulation described where the information should appear on the label and provided required language and structured sentences to include in the various label sections. The regulation also allowed omission of certain subsections if there were no data available or if the drug was not systemically absorbed. The primary goal of these labeling regulations was to inform counseling between a physician and a patient planning a pregnancy—to provide evidence-based, risk/benefit guidance prospectively, before an embryofetal exposure occurred. The regulations were not designed to address situations during which unplanned embryofetal exposure to the drug occurred inadvertently before pregnancy was known.

By 1997, FDA realized that the 1979 labeling regulations for pregnancy and nursing mothers had shortcomings and inconsistencies in practice. This was recognized both through FDA's 18-year work experience with the labeling regulations and through feedback from various professional organizations, such as the Teratology Society. In response, FDA sought feedback through a public hearing. At the hearing, FDA heard that the pregnancy categories were heavily relied on by clinicians but often misinterpreted and misused. Critics noted that:

- The pregnancy categories are often seen as a grading system, where the risk increases from lowest in category A to highest in category X, and that the risk/benefit considerations that define categories C, D, and X are not always appreciated by prescribers.

  For example, thalidomide and isotretinoin are category X drugs based on their risk for developmental toxicity—they are proven human teratogens with a high incidence of malformations following in-utero exposure. However, oral contraceptives are category X drugs because animal studies show developmental abnormalities and because there is no benefit to using the drug during pregnancy—a contraceptive cannot prevent pregnancy in a woman who already has an established pregnancy.

- Clinicians incorrectly assume that categories imply that drugs in a particular category carry a similar degree of risk for developmental abnormalities in humans and that the abnormalities are of similar type, severity, and incidence.

  For example, 65–70% of all drugs with a pregnancy category are category C. These drugs may have animal developmental toxicity studies that show positive findings in offspring or there may be no animal data at all. For category C drugs with animal studies, some drugs may show a low incidence of decreased fetal weights or delays in skeletal ossification in 1 species of animal; other drugs may show a high incidence of major structural malformations and/or embryofetal loss in 2 or 3 animal species. These differences in animal study outcomes may indicate differences in expected risk for developmental abnormalities in humans.

- The categories do not distinguish between supporting data from animals and humans.

  A category B drug may have animal studies that are negative but no adequate and well-controlled human studies. Or a category B drug may have adequate and well-controlled human studies that are negative but animal studies that are positive. It is not known whether these 2 sets of risk data carry a similar or different level of risk for a human embryo or fetus exposed to a drug or biologic in-utero.

Some speakers noted that the current pregnancy category system does not adequately address the full range of developmental toxicities (structural anomalies, functional deficits, embryofetal death, and alterations of growth). Others expressed concern about the failure of current regulations to adequately address inadvertent embryofetal drug exposures, which may contribute to termination of desired pregnancies even if the exposure risk is low. Experts requested that FDA clearly distinguish between risk information and clinical management information in pregnancy labeling.

THE EVOLUTION OF REVOLUTION: FDA'S PREGNANCY AND LACTATION LABELING INITIATIVE

Based on feedback from the 1997 public hearing, FDA decided to revise pregnancy and nursing mothers labeling and established a working group to develop a new model format. The working group included experts from multiple disciplines across the FDA Center for Drug Evaluation and Research (CDER), and the group carefully explored a wide variety of category system concepts to determine whether a different or more detailed category system could accurately communicate differences among drug-associated risks and benefits, or even risk alone. Working group members constructed evidence-based criteria that might underlie and define each category. However, when they applied these criteria to actual animal and human data for existing drugs with known risk profiles, none of the models produced clinically informative and reliable differentiations of risk among different drugs.

Consistent with FDA's approach to other aspects of product labeling, FDA concluded that:

- A category system is not appropriate to characterize and communicate the risks of drug use during pregnancy
- A narrative labeling model can best convey the potential risks of each drug or biologic based on available animal and/or human data.

Concepts of safety and risk are more complex in clinical medicine than in other settings, such as environmental exposure or consumer product safety. Clinical decision-making is particularly complex during pregnancy, when the risks and benefits of drug exposure must be considered both for the mother and her developing baby. 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. All prescribing and drug-use decisions in pregnancy require consideration of various clinical and individual factors including the potential effects of the drug on the mother and fetus, the severity of the mother's condition, maternal tolerance of the drug, coexisting maternal conditions, the impact of maternal illness on the fetus, and available alternative therapies.

The working group developed a narrative framework for pregnancy and nursing mothers labeling that included 3 informational elements: a risk summary, a clinical considerations (management) section, and a data section. This approach separated clinical advice from risk information in the labeling as requested by experts caring for women during pregnancy and the childbearing years. FDA then sought input on the labeling model at 2 advisory committee meetings and from clinicians (obstetricians/gynecologists, family practitioners, and nurse midwives) through focus group testing. Clinicians made it clear that they wanted human data in the label (even if limited), relevant clinical management information, and animal data described in terms of human exposures. They wanted the information presented using clear and precise language. Advisory committee members suggested that the risk summary would provide the most important information and should come first, and that the clinical considerations section should provide information in a nondirective way, since clinicians need to make decisions consistent with current standards of care that may change over time. They stated that the labeling should convey the relevance of animal study data to human pregnancy outcomes and the difference between situations where there are limited data versus no data.

FDA'S SECOND-GENERATION PREGNANCY AND LACTATION LABELING REGULATIONS: UNDERSTANDING THE PROPOSED RULE

The Proposed Rule describes a well-organized, structured framework in which to clearly communicate available data on the potential risks of drug and biologic use during pregnancy and lactation. Its careful development reflects changes and advances in drug science, clinical therapeutics, and maternal fetal medicine over the past 30 years. The proposed regulations would remove the letter pregnancy category from the labeling for all drugs. All drugs required to comply with the PLR regulations would be required to follow the format and content requirements and implementation schedule described in the Final Rule for Pregnancy and Lactation Labeling.

Under the proposed regulations, the pregnancy and lactation subsections of labeling would always be required, even for drugs that are not systemically absorbed, and would include 3 major informational parts:

- Risk summary
- Clinical considerations
- Data

When available, pregnancy registry contact information would appear at the beginning of each pregnancy labeling section, which would be followed by a standard statement about the background risk of birth defects, pregnancy loss, and other adverse outcomes that exist for all pregnancies regardless of drug exposure. As proposed, the regulations would place information about drug use during labor and delivery under "Pregnancy, Clinical Considerations," and would rename the nursing mothers section

Table 2: Summary of Proposed Pregnancy Labeling Regulation

Element	Content
Pregnancy registry statement	If available, contact information for pregnancy registry
Background risk statement	"All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes (*name of drug*)'s potential to increase the risk of developmental abnormalities above the background risk."
Fetal risk summary	Based on all available data, this section characterizes the likelihood that the drug increases the risk of developmental abnormalities in humans and other relevant risks. More than 1 risk conclusion may be needed. **For drugs that are systemically absorbed**: ■ When there are human data, a statement describes the likelihood of increased risk based on this data (framework for statement provided in proposed rule). This statement is followed by a brief description of the findings. ■ A standard statement describes the likelihood of increased risk based on animal data (not predicted to increase risk, low likelihood, moderate likelihood, high likelihood, or insufficient data). **For drugs that are not systemically absorbed**: ■ "(*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 drug."
Clinical considerations	This section provides information on the following topics: ■ **Inadvertent exposure** (known or predicted risk to the fetus from inadvertent exposure to drug before pregnancy is known) ■ **Prescribing decisions** for pregnant women: ● Describe any known risk to the pregnant woman and fetus from the disease or condition the drug is intended to treat. ● Information about dosing adjustments during pregnancy ● Maternal adverse reactions unique to pregnancy or increased in pregnancy ● Effects of dose, timing, and duration of exposure to drug during pregnancy ● Potential neonatal complications and needed interventions ■ **Drug effects during labor and delivery**
Data	Human and animal data are presented separately, with human data presented first. ■ Describes study type, exposure information (dose, duration, timing), and any identified fetal developmental abnormality or other adverse effects ■ For human data, includes positive and negative experiences, number of subjects, and duration of study ■ For animal data, includes species studied and describes doses in terms of human dose equivalents (provide basis for calculation)

"Lactation." *Tables 2* and *3* provide a detailed description of the key format and content elements in the proposed rule for pregnancy and lactation labeling.

At the time of publication, the proposed rule began a 90-day public comment period. Sometimes comment periods are extended, if needed, based on requests made to the Agency. During the open-comment period, individuals and groups can submit public comments to FDA on the Proposed Rule. FDA then carefully reviews and considers all of the comments and determines whether any format and/or content changes should be made to the proposed regulations. The Final Rule will present FDA's thinking on and decision regarding each of the submitted comments followed by the new regulations. Before publishing, the Final Rule will go through the usual clearance process. The time course for this process will be influenced by the volume and content of the comments and by the types of changes made to the proposed regulations.

ENHANCING WELL INFORMED USE OF MEDICINE DURING PREGNANCY AND BREASTFEEDING IN THE 21ST CENTURY

FDA believes that when finalized, the proposed content and format requirements for pregnancy and lactation labeling will positively impact the public health of women and their offspring. Under the proposed regulations, pregnancy and lactation labeling

Table 3: Summary of Proposed Lactation Labeling Regulation

Element	Content
Risk summary	For drugs that are not systemically absorbed, there is a standard statement stating that maternal use is not expected to result in infant exposure. For drugs that are systemically absorbed, the risk summary describes the following information or states that it is not available: ■ Effects of drug on milk production ■ Presence of drug in human milk ● If drug not detected, state limits of assay ● If drug is detected, provide drug concentration in milk and estimated infant daily dose (actual and compared to pediatric or maternal doses) ● Effects of the drug on the breast-fed child ■ If data shows that the drug does not affect the quantity and quality of breast milk and there is reasonable certainty that either the drug is not detectable in breast milk or will not adversely affect the breast fed child, then state: ● "The use of (*name of drug*) is compatible with breastfeeding."
Clinical considerations	This section must provide, when available, information on: ■ Ways to minimize exposure of the breast-fed infant to the drug ■ Dosing adjustments during lactation
Data	This section must provide an overview of the data that are the basis for information in the risk summary and clinical considerations.

would clearly and comprehensively present what is (and is not) known about medicine use in these populations. Labeling that is accessible to clinicians and relevant to clinical practice will facilitate well-informed risk/benefit decision-making and prescribing for women who are pregnant, breastfeeding, or of childbearing potential.

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