

# Teratology Public Affairs Committee Position Paper: Pregnancy Labeling for Prescription Drugs: Ten Years Later

Public Affairs Committee of the Teratology Society

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## HISTORICAL PERSPECTIVE

September 12, 2007 marks the tenth anniversary of a public hearing that was hoped to be the death knell of the pregnancy labeling categories for pharmaceuticals, the A, B, C, D, X system of designations that was put in place by the US Food and Drug Administration (FDA) in 1979 (US FDA, 1979). The replacement of the pregnancy labeling categories had been sought by the Public Affairs Committee of the Teratology Society, and the public hearing that was believed to herald the impending demise of the system in 1997 was seen as an important public health advance. On this tenth anniversary, the system remains in place, although some progress has been made in replacing it. We examine here the history of and rationale behind the effort to change the pregnancy label and the current status of proposed new labeling, and we offer recommendations for the future.

## Development of the Categories

The possibility that medication taken during pregnancy could produce congenital anomalies became more widely understood with the description of thalidomide embryopathy in 1961. There followed increasing interest in testing medications for teratogenic potential prior to marketing, and regulatory agencies in many countries had adopted or rewritten testing requirements by the end of the 1960s. As a consequence of the increase in experimental animal developmental toxicity testing and the increase in reporting on human pregnancy outcomes, clinicians in the 1970s were faced with an increasing amount of information derived from test systems the clinicians did not understand and from human reports of varying quality and utility.

The pregnancy labeling categories were introduced by the FDA to standardize the presentation of experimental animal and human data on potential pregnancy effects of medications and to provide a risk-benefit formula for practitioners. Arrival of the categories was trumpeted by *FDA Consumer*: "New labeling regulations to become effective later this year will make it easier for the doctor to determine the safety of a prescription drug for the use

intended. Rx labeling for physicians will be required to carry pregnancy precautions for protection of mother and fetus" (Hecht, 1979). The categories are prescribed by federal regulation (Code of Federal Regulations, 1997). Manufacturers are required to include the categories in the label of any medicinal product unless that product is not systemically absorbed and is known not to "have the potential for indirect harm to the fetus." The pregnancy category labeling contains two components, a letter designation and text that is determined by the letter designation. For four of the categories, the required text includes a statement intended to assist the practitioner in management of medication use in pregnant women (Table 1).

## The First Public Affairs Committee Position Paper

Teratology Society members who counseled patients on drug use during pregnancy did not find the categories to be helpful. In fact, it was the opinion of many clinicians that the inflexible use of prescribed language in pregnancy categories created patient and physician anxiety, which was compounded by the assumption that the categories represented a gradation of risk. The lack of information about the nature, severity, timing, or treatability of the putative fetal damage that resulted in a Category D or X classification was also viewed as a shortcoming of the pregnancy categories.

The Public Affairs Committee of the Teratology Society sponsored a symposium on the FDA classification of drugs on July 1, 1992 (Friedman, 1993). During this symposium, several speakers presented the deficiencies of the FDA system and discussed their belief that the alarmist features of this system led to unnecessary termination of wanted pregnancies. The final speaker in the symposium was Dr. Paula Botstein from the Center for Drug Evaluation and Research of the FDA, who thanked the Society for its input but indicated that the agency had no plans to change the system. One of the symposium participants

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Table 1  
Management Statements in the Pregnancy Category Labeling

Category	Statement
A	None
B	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
C	(Name of drug) should be given to a pregnant woman only if clearly needed
D	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 the fetus
X	(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 the fetus

From the Code of Federal Regulations (1997) 21 CFR 201.57.

later observed that a new pharmaceutical causing as many fetal deaths as are caused by the FDA pregnancy categories would never be allowed on the market (Scialli, 1992).

In June 1994, the Public Affairs Committee of the Teratology Society published a position paper called "FDA Classification of Drugs for Teratogenic Risk", which stated, "The Teratology Society recommends that the FDA Use-In-Pregnancy ratings be deleted from drug labeling and replaced by narrative statements that summarize and interpret available data regarding hazards of developmental toxicity and provide estimates of teratogenic risk" (Public Affairs Committee, 1994).

### The 1997 Public Hearing

In part as a result of the Teratology Society's efforts, FDA officials became interested in revising the pregnancy labeling system for medications. An early step in the process was the convening of a public hearing on the content and format of labeling on September 12, 1997. The hearing was chaired by Janet Woodcock, then Director of the Center for Drug Evaluation and Research.

With few exceptions, the presentations that day were uniform in identifying the pregnancy categories as a source of inaccurate counseling. Teratology Society members were among those making presentations. John DeSesso, a past president of the Teratology Society, pointed out that the pregnancy categories did not address the time in gestation when an adverse effect may be produced, an important element in evaluating the risk of an exposure. Bob Brent, another past president, spoke about the anxiety-provoking nature of current label language. Katherine Wisner gave a practitioner's viewpoint, telling the FDA panel that it is important to improve labeling because practitioners rely very heavily on the pregnancy categories to make decisions.

An FDA summary of the points raised at this meeting included:

- The categories are routinely relied upon in clinical decision making because they appear to provide a simple, convenient measure of risk.
- The categories are confusing and overly simplistic and are not adequate to communicate risk.
- The categories convey the incorrect impression that risk increases from A to B to C to D to X.
- The categories create the incorrect impression that drugs within the same category have similar potential to cause toxicity.

- The current labeling does not discriminate between potential adverse effects on the basis of severity, incidence, or type of effect or on the basis of dose, duration, frequency, route, and gestational timing of exposure.

- The current label inadequately addresses inadvertent exposures, focusing instead on planned prescribing (US Food and Drug Administration, 2006).

The 1997 hearing prompted FDA to undertake a revision of its pregnancy labeling regulations. A model format was developed that would replace the pregnancy categories with clearer and more complete text summaries of available information on risk. The model format was evaluated by focus groups of clinicians and by FDA Advisory Committees.

## CURRENT STATUS

### New Label, Old Categories

On January 25, 2006, the requirements on format and content of much of the product label were revised. The new label was designed to be more easily read and interpreted by clinicians and consumers. The new label requirements did not include changes to the pregnancy labeling, although the pregnancy section was relocated from "Precautions" to "Use in Specific Populations." This change in labeling was implemented with the old pregnancy categories still in place because of the perceived need to clarify the nonpregnancy portions of the label sooner than the revisions in the pregnancy portion of the label would be ready.

### The Proposed Rule

The FDA has drafted a Proposed Rule that would completely overhaul the pregnancy and lactation portions of the product label. At this writing, the draft Proposed Rule has not been approved and released for public comment. When and if the draft Proposed Rule is approved, public comments will be solicited and used in the writing of a Final Rule. If the Final Rule is similar to the draft Proposed Rule, the new label will require the following sections:

1. Information on pregnancy registries, if any, for the product and how the registries can be contacted.
2. A general statement about background risk of adverse pregnancy outcome.
3. A "Fetal Risk Summary" containing a narrative description of the risks of use of the medication, includ-

Table 2  
Risk Conclusion Language from the FDA Draft Proposed Rule

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Human data

- 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)"
- 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 developmental abnormality)"

Experimental animal data

- 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
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ing a characterization of the likelihood that the drug increases the risk of abnormal development. The types of developmental outcomes to be considered include structural malformations, miscarriage, stillbirth, neonatal death, functional abnormalities, and alterations to growth. The conclusions about risk will use standardized statements (discussed below). If a drug is considered contraindicated during pregnancy, details will be given about the circumstances under which the drug is contraindicated. For example, a drug might be contraindicated for one indication but not for another, or it might be contraindicated during one portion of pregnancy but not all of pregnancy.

4. A discussion of "clinical considerations" to specifically and separately address inadvertent exposures, prescribing decisions for women known to be pregnant, and considerations relevant to use of the medication during labor and delivery. Considerations of risks from untreated disease would also be incorporated in this section. This portion of the label would include information about dose adjustments during pregnancy.

5. A summary of the data underlying the fetal risk summary and clinical consideration sections.

### The New Categories

Although the draft Proposed Rule does not include categories, the proposed fetal risk summary would include standardized language that will give rise to de facto categories (Table 2). When the fetal risk summary is based on experimental animal studies, which is expected for most medications, the likelihood of risk will be categorized as none, low, moderate, high, or unknown. Experimental teratologists will read the examples in Table 2 with the concern that these criteria will be inflexibly applied to data sets, forcing new medications into the none, low, moderate, or high categories much as new

medications are now shoe-horned into the A, B, C, D, X categories.

Standardized language is a common feature of government regulation. Standardization of language may also be welcomed by industry scientists and label-writers who find it easier to comply with the rules when the rules are sufficiently clear. It remains to be seen whether the criteria for each category are interpreted with sufficient flexibility to result in scientifically sound risk communication. It is an improvement that the fetal risk summary does not automatically call up a clinical recommendation, as does the current categorical language (Table 1). In spite of the use of categorical language, the proposed new system appears to offer important advantages over the current system. For example, in the current system, Category X is a nonspecific designation that a medication is contraindicated during pregnancy. The new labeling system will provide information on why the drug is contraindicated and the circumstances (dose, indication, gestational time) under which the drug is contraindicated. Other advantages include the addition of information on registries, the conscientious attention to clinical considerations, and an enhanced opportunity for a risk/benefit analysis. The FDA physicians and scientists who developed the proposed system should be congratulated for so thoroughly addressing the concerns that were raised about the current label.

### RECOMMENDATIONS

The draft Proposed Rule describes a label that appears to be superior to the current pregnancy categories. The introduction of new de facto categories may represent a necessary limitation; however, the new label will provide practitioners and consumers with the opportunity to read a substantial amount of explanatory text, including clinical considerations that are not keyed directly to the risk summary.

The Public Affairs Committee of the Teratology Society makes the following recommendations:

1. The draft Proposed Rule should be approved and released for public comment without further delay. At present, the FDA estimates that the new system will not become effective before June 30, 2010, 13 years after the public hearing, an unreasonably distant date given the recognized deficiencies of the current system.

2. The categorical language prescribed in the draft Proposed Rule should be applied flexibly so that the label represents a scientifically sound interpretation of the underlying data. The categorical language should be accompanied by the reason for the selection of the specific risk designator, for example: "Based on the animal data, the likelihood of developmental abnormalities is predicted to be low because the developmental defects were only seen in the mouse, and this effect was considered to be species-specific".

3. Before and after implementation, the new system should be tested using practitioners and consumers. Although the new system looks good on paper, it will be important to determine whether or not it results in effective risk communication and appropriate clinical decision-making.

4. A mechanism should be developed by which the labeling system can be improved more easily. The deficiencies of the pregnancy categories were recognized by the FDA more than a decade ago, yet at this writing, the categories are still in place. It should not take so long to fix such a flawed system.

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