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Food and Drug Administration
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RE: Comments on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling

The 3 million volunteers and 1500 staff members of the March of Dimes Foundation appreciate the opportunity to submit the Foundation's comments on the *Food and Drug Administration's (FDA) proposed rule on the content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling*. The March of Dimes is a national voluntary health agency founded in 1938 by President Franklin D. Roosevelt to prevent polio. Today, the Foundation works to improve the health of mothers, infants and children by preventing birth defects, premature birth and infant mortality through research, community services, education, and advocacy. The March of Dimes is a unique partnership of scientists, clinicians, parents, members of the business community, and other volunteers in 51 chapters in every state and Puerto Rico.

The March of Dimes applauds the continuing effort of the FDA to modernize the archaic prescription drug and biological products pregnancy and lactation labeling requirements. We commend the FDA for initiating a multi year analysis of drug labeling and encourage swift adoption and implementation of the proposed rule which would go a long way to ensure that health care providers have comprehensive, current and easy to decipher scientific data on the harms and benefits of prescribing prescription drugs and biological products during the continuum of care for women from preconception to postpartum.

Unfortunately, current labeling does not provide information about the effects of inadvertent drug exposure before a woman knows she is pregnant and since 50% of pregnancies are unplanned, the Foundation strongly supports the proposed rule requiring the labeling to contain the known or predicted risks to the fetus from inadvertent exposure to the drug including human or animal data on dose, timing, and duration of exposure. This is important because for many drugs with teratogenic potential, the levels of evidence varies widely based on available animal or human data. The severity, incidence and type of teratogenic risk that is posed by the drug can vary based on dosage, timing and duration of exposure. For example in a recent population-based study examining prenatal exposure to serotonin reuptake inhibitors, researchers found that the length of in utero exposure, instead of timing, increased risk for adverse neonatal outcomes.¹ Having such information is important for physicians to be able to effectively meet the challenge of communicating risk prediction with their patients.

Numerous animal- and population-based studies showing the teratogenic effects of specific prescription drugs exist in the literature. These drugs include those with strongly established risks of birth defects such as isotretinoin, used to treat severe cystic acne; thalidomide, used to treat skin lesions in leprosy as well as a cancer of plasma cells called multiple myeloma; and valproic acid, an antiepileptic drug.^{2,3} Others, such as studies of prescription drugs for depression, have had mixed outcomes and therefore require careful consideration to weigh the risks to the fetus and infant when considering the potential benefits to the pregnant woman or new mother.⁴ Reproductive-aged women and their physicians should be aware of the potential teratogenic and developmental risks of drugs prescribed for chronic conditions such as epilepsy, depression and dermatologic problems that may pose a danger to the fetus and infant if taken at the time of conception, during pregnancy or breastfeeding. In a 2007 study examining communication between doctors and patients, nearly half of the 500,000 women were not counseled by their doctor about the potential teratogenic effects of particular prescription drugs.⁵ This makes the efforts of the FDA to improve the labeling of drug information even more critical and useful in order to provide easy access to information that empowers women of childbearing age to become more informed health care consumers.

Clinical decision making is the most important aspect of the doctor-patient relationship. In order to optimize communication, it is imperative that a healthcare provider has the most up to date scientific information. The proposed rule would make it mandatory for labels to include information about fetal risk summary, clinical considerations and human and animal data so that healthcare providers can make well informed decisions. The March of Dimes recommends that the fetal risk summary and clinical considerations precede the pregnancy registry contact information because the clinical data on risks and potential harms to the fetus is far more important and should be the first item that health care providers address before discussing pregnancy registries with their patients.

The Foundation supports pregnancy registries as important tools to help researchers track women consuming specific drugs and the potential effects that these drugs may have on the pregnancy, fetus, and infant. The March of Dimes supports the proposed rule requiring labels to include information about existing pregnancy registries because often times women are not aware that a registry exists and providing this information will afford them the opportunity to not only learn more, but also to consider enrolling in a registry.

In situations where human data exists but is limited, the March of Dimes defers to the FDA's working group findings and their determination that the use of low, moderate or high to classify risk would be more helpful in fetal risk summaries than the format of standardized risk conclusions. However, when considering different levels of risk based on animal data and their potential relevance to human fetal effects, the March of Dimes believes that the use of standardized statements to communicate different levels of risk can be helpful. Combined, the statements found in the fetal risk summary are helpful in declaring how much of the evidence used to communicate the drug's risk is reliant on animal data alone or in conjunction with human data. It also provides expert opinion on the severity of risk to clinicians who may not be expert in such assessments. Finally, the

March of Dimes does not feel additional information such as information on the number of animal species with positive findings or the consistency and severity of such findings needs to be included in the Data component of labeling.

The March of Dimes applauds the work done by FDA and appreciates the opportunity to submit recommendations on *Food and Drug Administration's (FDA) proposed rule on the content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling*. We hope you will embrace our recommendations to improve the health of pregnant women.

References:

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3. Battino D, Tomson T. Management of epilepsy during pregnancy. *Drugs*. 2007;67(18):2727-46.
4. ACOG Practice Bulletin No. 92. Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol*. 2008 Apr;111(4):1001-20.
5. Schwarz EB et. al. Documentation of contraception and pregnancy when prescribing potentially teratogenic medications for reproductive-age women. *Ann Intern Med*. 2007 Sep 18;147(6):370-6.