



POLICY STATEMENT REGARDING CONTRACEPTIVE USE

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The Duke University Health System Institutional Review Board (DUHS IRB) has determined that all females and males of reproductive potential being considered for participation in a research study where a possibility of harm to a fetus exists must practice appropriate contraceptive measures before undergoing any study-related activities that might harm a developing fetus. Appropriate contraceptive measures must be maintained until all known risks to the fetus have ended.

Clear language explaining the necessity for appropriate contraceptive measures and providing examples of acceptable methods for females and males must appear in the informed consent documents for a research study. Standard language for use in informed consent documents, including a listing of medically acceptable contraceptives, may be found at the IRB web site.

The FDA uses five categories, designated as A, B, C, D and X, to classify risk associated with drug use in pregnancy [21CFR201.57]. The regulations require specific drug labeling for each of the risk categories.

- **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 shall 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." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall 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*)."
The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.
- **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 shall 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 during 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 shall 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." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

- **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 shall state: "Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall 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." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.
- **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 (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See `Warnings' section." Under the "Warnings" section, the labeling states: "*(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 the fetus."

- **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 (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See `Contraindications' section." Under "Contraindications," the labeling shall 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 the fetus."

The IRB requires 2 approved forms of contraception, for females, while enrolled in clinical studies that utilize category D or category X drugs. For males enrolled in studies that utilize category D or category X drugs, the IRB does not necessarily require the use of two forms of contraception, unless the drug in question is toxic to sperm in a manner that would lead to birth defects.

When there is *no information* available on the spermatotoxicity of the category D or category X drug, or the semen concentration levels of the drug in males, then 2 approved forms of contraception are required for males enrolled in studies utilizing category D or category X drugs.

For drugs with residual effect, investigators must specify in the consent form the period of time following study participation (weeks/months) that subjects should continue using 2 forms of contraception. Investigators should consider adding some consent form language that discourages sexual activity that leads to conception during the time of study participation for subjects receiving category D or X drugs.

In the review of a protocol, the IRB Primary Reviewer will make note of the FDA Pregnancy Category designated for the drug(s) to be used in a proposed study.

The IRB may require the use of IRB standard contraceptive language in a study's informed consent documents based on the FDA Pregnancy ratings assigned to the drug(s), the potential risk to a developing fetus, and the research evidence (or lack of evidence) pertaining to mutagenic and teratogenic effects in humans.