This is the information that I promised to send you during our recent telephone conversation.

FDA has previously been asked how pregnancies of female study subjects should be reported, whether informed consent of a male subject's female partner is required to collect information about a pregnancy of the female partner, and the follow up that should be done. In general, if there is a specific situation to be addressed, we recommend contact with the review division with responsibility for reviewing the drug product, so that the review division can provide additional guidance.

Question 1a: Is a Sponsor required to collect ... information [regarding how pregnancies of female partners of male subjects should be reported] regardless of compound?

Answer 1a: FDA does not have specific regulations or guidance about reporting pregnancies of female partners of male subjects, although FDA has occasionally been asked how pregnancies in female study subjects should be reported. In those cases, we have referred to the ICH E8 Guidance, at Section 3.1.4.3, "Special Populations," which states:

"Some groups in the general population may require special study because they have unique risk/benefit considerations that need to be taken into account during drug development, or because they can be anticipated to need modification of use of the dose or schedule of a drug compared to general adult use... Particular attention should be paid to the ethical considerations related to informed consent from vulnerable populations and the procedures scrupulously followed (see ICH E6).

"(a) Investigations in pregnant women. In general, pregnant women should be excluded from clinical trials where the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow up evaluation of the pregnancy, fetus, and child is very important. Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, follow up of the pregnancy, fetus, and child is very important."

In keeping with ICH E8, FDA would expect sites to report the pregnancy of a female subject to the sponsor, the IRB/EC, and the agency. In the past, we have recommended that the female subject receive counseling (particularly if there is any information about the risks to the fetus, or if there is NO information about fetal exposure or information that can be derived from animal studies, ensuring that she is aware of that). If the female subject chooses to continue the pregnancy, then FDA routinely recommends that she be asked to allow the investigator to follow her pregnancy to term (or longer if possible for developmental sequelae), so that any important safety information could be obtained. If you want to read the ICH E8 guidance in its entirety, here is the link: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/G
FDA does not have any specific requirements or guidance on data that should be collected to support the presence or absence of contraception recommendations or requirements in labeling or as part of a Risk Evaluation and Mitigation Strategy (REMS) when the male partner is using a known or suspected teratogen. However, FDA is in the process of reviewing its recommendations related to advice about contraceptive methods to be used by male subjects who participate in FDA regulated research.

Question 1b: Is [collection of such information] truly dependent on the pre-clinical/clinical background of the compound?

Answer 1b: As stated above, FDA does not have specific regulations or guidance about collecting such information. However, there may be compelling circumstances that warrant further consideration or discussion, particularly if pre-clinical data suggests that a product may have some teratogenic effects. For example, in order to limit fetal exposure to thalidomide, a known teratogen, the product labeling states that a male patient must agree to abstain from heterosexual sexual contact or use a latex condom when he engages in sexual contact with a woman who can become pregnant or who is pregnant.

You might find it helpful to review some of the existing pregnancy registries to see the kinds of questions that are being asked (e.g., National Transplantation Pregnancy Registry). Here is a link to FDA's list of Pregnancy Exposure Registries: http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm.

Questions 2 and 3: What information can sponsors collect about the female partner? Is consent from the female partner required in order for health information to be collected?

Answer to 2 and 3: Informed consent must be obtained from the female partner before any information may be collected about her, and if informed consent is not obtained, no information may be collected. Any informed consent document or procedures to be used for this purpose should be reviewed and approved by the IRB or ethics committee responsible for reviewing the study. See also the answer to question 4, below.

Question 4: Are Sponsors required to collect information regarding the pregnancies via the Investigator or is direct contact with the female partner allowed?

Answer to 4: 21 CFR 50.20 states:

"Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient
opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."

FDA would recommend that the IRB carefully review procedures for obtaining consent, to ensure that the circumstances under which consent is obtained are not coercive or intimidating to the female partner of the study subject. FDA would recommend that consent be obtained by the site, rather than through direct contact with the sponsor.

One other thing thing--FDA also issued the "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072044.pdf). The primary concern of this guidance is the inclusion or exclusion of women of childbearing age in clinical trials. It does NOT address what to do should a study subject become pregnant during a trial, but may nevertheless be of interest to you.

I hope this rather lengthy discussion is helpful, and again, would recommend if you have additional questions or need advice about how to approach a specific situation, that you contact the review division with jurisdiction over the product in question.

Sorry it took so long, but FDA recently revised its website so I had to relocate all of the documents to make sure the links were accessible.

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