Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact the Division of Pediatric and Maternal Health (CDER) at (301) 796-2200 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations about how and when to include pregnant women in drug development clinical trials for drugs and biological products based on the Food and Drug Administration's (FDA's or Agency's) current thinking on this subject.[2] Specifically, this guidance supports an informed and balanced approach to gathering data on the use of drugs and biological products during pregnancy through judicious inclusion of pregnant women in clinical trials and careful attention to potential fetal risk. This draft guidance is intended to serve as a focus for continued discussions among various entities such as the Agency, pharmaceutical manufacturers, the academic community, institutional review boards (IRBs), and others who are involved with the conduct of clinical trials in pregnant women.[3]

This guidance discusses the scientific and ethical issues that should be addressed when considering the inclusion of pregnant women in drug development clinical trials. From a scientific and ethical standpoint, the population of pregnant women is complex based on the interdependency of maternal and fetal well-being, and the need to take into consideration the risks and benefits of a drug to both woman and fetus (American College of Obstetricians and Gynecologists 2015). The scientific and ethical issues discussed in this guidance apply both to clinical trials that enroll pregnant subjects and to clinical trials that allow enrolled subjects who become pregnant to remain in the trial.

[1] This guidance has been prepared by the Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research and the Office of Good Clinical Practice, Office of Special Medical Programs, in the Office of the Commissioner at the Food and Drug Administration.

[2] Throughout this guidance, the term *drug* means drug and biological products regulated by CDER or CBER.

[3] In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during drug development.

Some of the information provided in this guidance applies to drugs indicated to treat pregnancy-specific conditions (e.g., preterm labor, pre-eclampsia), but the larger focus is on drugs indicated for conditions that occur commonly among females of reproductive potential. Women in this group may require treatment for chronic disease or acute medical problems, and may become pregnant multiple times during the reproductive phase of their lives.

This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials*, *E10 Choice of Control Group and Related Issues in Clinical Trials*,[4] and the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*.[5] The draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*[6] and certain disease-specific and drug class-specific guidances may provide additional considerations for studying pregnant women during drug development.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the interests of promoting maternal/fetal health and informed prescribing decisions during pregnancy, this guidance addresses the challenges of including pregnant women in drug development research. There are more than 60 million women in the United States between the ages of 15 and 44 years, and almost 4 million births per year (U.S. National Vital Statistics Reports). Like women who are not pregnant, some pregnant women need to use drugs to manage chronic disease conditions or treat acute medical problems. To the extent there is labeling information for pregnant women, it is usually based on nonclinical data with or without limited human safety data. The frequent lack of information based on clinical data often leaves the health care provider (HCP) and the patient reluctant to treat the underlying condition, which in some cases may result in more harm to the woman and the fetus than if she had been treated. In addition, pregnant women often use medically necessary drugs without a clear scientific understanding of the risks and benefits to themselves or their developing fetuses (Lyerly et al. 2008).

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs or Biologics guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

[6] When final, this guidance will represent the FDA's current thinking on this topic.

Currently, information about drug use in pregnancy generally is collected in the postmarketing setting, using data from observational studies such as pregnancy exposure registries and other cohort studies, case control studies, and surveillance methods. Historically, there have been barriers to obtaining data from pregnant women in clinical trials in an effort to protect them and their fetuses from research-related risks. However, in certain situations, it may be helpful to collect data in pregnant women in the setting of a clinical trial (Goldkind et al. 2010). For example, it may be useful to compare the safety and efficacy of a drug that has been considered the standard of care for pregnant women with a newer treatment (Jones et al. 2010). In other situations, a woman's health and the well-being of her fetus may benefit from clinical trial participation. For example, a pregnant woman may need access to experimental therapies in a clinical trial setting because there are no approved treatment options available. Sometimes a drug treatment offered only through a clinical trial will hold out the prospect of direct benefit to the pregnant woman and/or her fetus beyond otherwise available therapies. For example, some clinical trials for drugs that treat human immunodeficiency virus (HIV), tuberculosis, and malaria enroll pregnant women (or provide that patients who become pregnant can continue enrollment) based on ethical principles and clinical need.

There are multiple reasons for considering the inclusion of pregnant women in clinical trials, including the following:

- Women need safe and effective treatment during pregnancy
- Failure to establish the dose/dosing regimen, safety, and efficacy of treatments during pregnancy may compromise the health of women and their fetuses
- In some settings, enrollment of pregnant women in clinical trials may offer the possibility of direct benefit to the woman and/or fetus that is unavailable outside the research setting
- Development of accessible treatment options for the pregnant population is a significant public health issue

Extensive physiological changes associated with pregnancy may alter drug pharmacokinetics and pharmacodynamics, which directly affects the safety and efficacy of a drug administered to a pregnant woman through alterations in drug absorption, distribution, metabolism, and excretion.[7] Pregnancy-related changes in various organ systems (e.g., gastrointestinal, cardiovascular, and renal) also may alter drug pharmacokinetics and pharmacodynamics. For example, a 30 to 40 percent increase in glomerular filtration rate results in much higher rates of clearance for some drugs during pregnancy (Mattison and Zajicek 2006); therefore, prescribing often occurs in the absence of knowledge regarding the dose required to achieve the desired therapeutic effect (Andrew et al. 2007).

[7] See the draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling.*

Filling the knowledge gaps regarding safe and effective use of drugs in pregnant women is a critical public health need, but one that raises complex issues.

III. ETHICAL CONSIDERATIONS

The inclusion of pregnant women in clinical trials is guided by human subject protection regulations and involves complex risk-benefit assessments that vary depending on the seriousness of the disease, the availability of other treatments, the trial design, and whether the proposed investigation will occur in the premarketing or postmarketing setting. Because of the complex ethical issues involved in designing clinical trials that include pregnant women, sponsors should consider including an ethicist in planning their drug development programs. Moreover, sponsors should consider meeting with the appropriate FDA review division early in the development phase to discuss when and how to include pregnant women in the drug development plan. These discussions should involve FDA experts in bioethics and maternal health.

A. FDA Regulations That Govern Research in Pregnant Women

FDA-regulated clinical trials in pregnant women must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR part 56, Institutional Review Boards, and 21 CFR part 50, subpart B, Informed Consent of Human Subjects). In addition, if the trial is supported or conducted by the Department of Health and Human Services (HHS), then 45 CFR part 46 may also apply, which would include subpart B, Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.[8] The FDA regulations do not contain a section similar to 45 CFR part 46, subpart B; however, the FDA recommends that these requirements be satisfied for FDA-regulated clinical research. Subpart B requires that trials supported or conducted by HHS meet all of the following 10 conditions:

1. Where scientifically appropriate, nonclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal[9] and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

3. Any risk is the least possible for achieving the objectives of the research;

[8] See 45 CFR 46.204.

[9] See section III.B., Research-Related Risks, for discussion of minimal risk.

4. The pregnant woman's consent is obtained in accord with the informed consent provisions of 45 CFR part 46, subpart A;

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of 45 CFR part 46, subpart A, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;

6. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

7. For children as defined in § 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of 45 CFR part 46, subpart D;

8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

10. Individuals engaged in the research will have no part in determining the viability of a neonate.

IRBs are required to possess the professional competence necessary to review the specific research activities that they oversee (21 CFR 56.107(a)). IRBs must include persons who are knowledgeable in areas about the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice (21 CFR 56.107(a)). Therefore, if an IRB regularly reviews research involving pregnant women, the IRB must consider including one or more individuals who are knowledgeable about and experienced in working with such subjects (21 CFR 56.107(a)). When an IRB considers whether to approve a protocol involving pregnant women, it should consider only those risks and benefits (direct to the subjects, or generalizable knowledge) that may result from the research itself (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research) (21 CFR 56.111(a)(2)). Additionally, IRBs are required to determine that additional safeguards are included in the trial to protect the rights and welfare of subjects who are pregnant (21 CFR 56.111(b)).

Additional issues are raised by pregnant minors. Depending on state law, a pregnant minor may be considered emancipated by virtue of her pregnancy, a mature minor, or still a child (see the definition of children under 21 CFR 50.3(o)). IRBs should be familiar with applicable law of the jurisdiction in which a trial will be conducted. In the event that a clinical trial regulated by the FDA allows the enrollment of pregnant minors, or a minor becomes pregnant while enrolled in a clinical trial, and the pregnant minor meets the definition of a child under applicable state law, the IRB would have to comply with the applicable requirements of 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

B. Research-Related Risks

Research-related risks may meet the regulatory definition for *minimal risk* or may involve greater than minimal risk. FDA regulations define minimal risk as follows (21 CFR 50.3(k)):

> "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Research-related risks are the risks specifically associated with the trial interventions or procedures. If a woman is assigned to receive a drug while enrolled in a clinical trial (i.e., the assignment of the drug is determined by the protocol), then the risks associated with the drug would be considered research-related.

In contrast, risks are not research-related when they are independent of the study and not associated with a trial intervention or protocol requirements. In other words, when a study collects data about drug treatment during pregnancy but the drug was prescribed before study enrollment by the patient's HCP, then the risks associated with the drug use are not research-related risks (Sheffield et al. 2014). For example, in a study in which the investigator plans to assess the pharmacokinetics of a particular selective serotonin reuptake inhibitor (SSRI) during pregnancy, the investigator enrolls pregnant women with a history of major depression who are currently managed on this drug. In this study the SSRI does not create research-related risk, because the patients are already using the SSRI (as previously prescribed by their HCPs) to manage their medical conditions. The only risks of the study are those associated with study-specific procedures (e.g., blood sample collection), and potential loss of confidentiality or privacy.

In this situation, the research-related risk to the fetus is minimal, and the purpose of the research is the development of important biomedical knowledge, which cannot be obtained by any other means. Some dedicated pharmacokinetic (PK) studies conducted with pregnant women (such as the previous SSRI example) can offer direct benefit to subjects if the data are used during the trial to adjust the dosing for individual subjects when clinically appropriate. The informed consent process should include discussion of expectations about whether trial data will be monitored and evaluated in a way that can potentially benefit the subject during the trial.

There may be circumstances in which a clinical trial can potentially expose a fetus to greater than minimal risk. Pregnant women can be enrolled in clinical trials that involve greater than minimal risk to the fetuses if the trials offer the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses. For example, this benefit may result from access to: (1) a needed but otherwise unavailable therapy (e.g., a new antituberculosis drug for multidrug resistant disease); or (2) a drug or biologic that reduces the risk for acquiring a serious health condition (e.g., a vaginal microbicide that reduces transmission of HIV and herpes simplex virus).

C. General Guidelines for Including Pregnant Women in Clinical Trials

This section provides general guidelines and considerations for including pregnant women in clinical trials. However, every drug development situation is unique, and individualized approaches to clinical trial design may be required to facilitate inclusion of pregnant women in specific drug development plans.

The FDA considers it ethically justifiable to include pregnant women with a disease or medical condition requiring treatment in clinical trials under the following circumstances:

<u>In the postmarketing setting (i.e., FDA-approved drugs)</u>

- Adequate nonclinical studies (including studies on pregnant animals) have been completed[10]

  and

- There is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women

  and one of the following:

- Efficacy cannot be extrapolated

  and/or

- Safety cannot be assessed by other study methods

<u>In the premarketing setting (i.e., investigational drugs)</u>

- Adequate nonclinical studies (including studies on pregnant animals) have been completed

  and

- The clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)

The above conditions would also apply to a drug that is being developed to treat a pregnancy-specific condition.

[10] The phrase *adequate nonclinical studies* refers to recommendations for the design and conduct of reproductive toxicology and other nonclinical studies described in the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

Women who become pregnant while enrolled in a clinical trial

When a pregnancy has been identified during a clinical trial, unblinding should occur so that counseling may be offered based on whether the fetus has been exposed to the investigational drug, placebo, or control. The risks and benefits of continuing versus stopping investigational treatment can be reviewed with the pregnant woman. Pregnant women who choose to continue in the clinical trial should undergo a second informed consent process that reflects these additional risk-benefit considerations.

If fetal exposure has already occurred, a woman who becomes pregnant while enrolled in a clinical trial should be allowed to continue on the investigational drug if the potential benefits of continued treatment for the woman outweigh the risks of ongoing fetal exposure to the investigational drug, of discontinuing maternal therapy, and/or of exposing the fetus to additional drugs if placed on an alternative therapy. Regardless of whether the woman continues in the trial, it is important to collect and report the pregnancy outcome.

IV. OTHER CONSIDERATIONS

Including pregnant women in a trial involves careful risk-benefit assessments. All trials must be designed to minimize risk as much as possible while preserving the ability to achieve the objectives of the research (21 CFR 56.111). Some general considerations for sponsors and investigators include:

- Obtaining adequate reproductive and developmental toxicology data in relevant nonclinical models
- Identifying the trial population that will derive the most benefit while trying to minimize risk
- Considering the gestational timing of exposure to the investigational drug in relation to fetal development
- Choosing appropriate control populations

Sponsors should also consider the issues discussed in the following sections when designing a clinical trial that will include pregnant women.

A. Disease Type and Availability of Therapeutic Options in the Pregnant Population

Sponsors should take into account the incidence of the disease, the severity of the disease (e.g., whether or not it is life-threatening), and the availability of other therapeutic options and their risks. Pregnant patients with no other viable therapeutic options (e.g., drug resistance, drug

intolerance, contraindication, drug allergy) to treat a serious or life-threatening disease or condition may be appropriate candidates to enroll in a clinical trial.

B. Timing of Enrollment

The most appropriate time to include pregnant women in clinical trials during drug development may differ. Nonclinical reproductive and developmental toxicology studies generally should be completed before enrolling pregnant women in clinical trials.[11] In general, phase 1 and phase 2 clinical trials in a nonpregnant population that include females of reproductive potential should be completed before sponsors enroll pregnant women in later phase clinical trials. Sponsors should consider whether any of the following situations apply in determining when to enroll pregnant women in the drug development process.

- *If there are limited safety data or other approved (i.e., safe and effective) treatments are available*: In this situation, it may be more appropriate to complete phase 3 clinical trials in a nonpregnant population before enrolling pregnant women and exposing them to the investigational drug

- *If there are limited therapeutic options*: In these situations, the risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials

- *If there are safety data for a drug that has been studied previously for other indications or populations*: In these situations, the risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials

C. Pharmacokinetic Data

Because of the extensive physiological changes associated with pregnancy, PK parameters may change, sometimes enough to justify changes in dose or dosing regimen. For drug development programs where there are plans to enroll pregnant women in a phase 3 clinical trial, PK data in pregnant women should be collected during the phase 2 clinical trials to guide appropriate dosing in phase 3. In situations where pregnant women are enrolled in phase 3 clinical trials for a marketed drug, PK data should be collected as part of the trial.

In appropriate situations, nonpregnant women who become pregnant while on the investigational drug and consent to remain on the drug can also consent to PK assessments at steady state to collect data on correct dosing during pregnancy. Modeling and simulation have been increasingly used to support the design of clinical PK studies (Xia et al. 2013; Ke et al. 2013). For PK studies including pregnant patients, physiological changes during and after pregnancy that are critical for drug absorption and disposition may need to be considered in the model.

For additional information on PK modeling, study design considerations, and PK studies in pregnant women, refer to the draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*.

[11] See ICH M3(R2).

D. Safety Data Collection and Monitoring

When pregnant women are enrolled in a clinical trial, data collection elements should include, at a minimum: gestational age at enrollment; gestational timing and duration of drug exposure; and pregnancy outcomes including adverse maternal, fetal, and neonatal events. Enrolled pregnant patients should also receive obstetrical care that meets the recognized standards of care. Infants born to mothers who were exposed to the investigational drug should have follow-up safety information collected. Systemic drug exposure to the fetus/newborn can be evaluated by collecting cord blood or neonatal levels of drug and/or metabolites, depending on the timing of exposure to the drug and its half-life.

Clinical trials that enroll pregnant women should include investigators or consultants who have expertise in obstetrics and/or maternal/fetal medicine, depending on the underlying conditions treated by the investigational drug.

All clinical trials require monitoring (21 CFR 312.50 and 312.56), and no single approach to monitoring is appropriate or necessary for every clinical trial.[12] Clinical trials that involve pregnant women should include a data monitoring plan that includes members with relevant specialty and perinatal expertise to permit ongoing recognition and evaluation of safety concerns that arise during the course of the trial. This facilitates appropriate, expert assessment of adverse event reports.

E. Stopping a Clinical Trial That Enrolls Pregnant Women

There may be situations where it would be appropriate to stop a randomized, controlled clinical trial that is enrolling pregnant women. Examples include the following:

- An appropriately planned interim analysis demonstrates superior efficacy of the control or active comparator arm.

- There are documented serious maternal or fetal adverse events that can be reasonably attributed to drug exposure and are deemed to exceed the potential benefits of drug treatment. This determination should include consideration of alternative effective treatments and the risks of the underlying condition.

[12] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* and the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring*.

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