COMMENTARY

JUNE 2018

FDA Draft Guidance Regarding Inclusion of Pregnant Women in Clinical Trials

IN SHORT

The Situation: Pregnant women have historically been excluded from clinical trials due to concerns about the potential for adverse effects on pregnant women and their fetuses.

The Development: The U.S. Food and Drug Administration ("FDA") has issued draft guidance providing recommendations about how and when pregnant women should be included in clinical trials for drugs and therapeutic biological products that are regulated by FDA's Center for Drug Evaluation and Research or FDA's Center for Biologics Evaluation and Research (referred to throughout the guidance and this *Commentary* as "drugs").

Looking Ahead: FDA encourages sponsors and investigators to consider inclusion of pregnant women in clinical trials pursuant to FDA's support of an "informed and balanced" approach to gathering data on the use of drugs during pregnancy through "judicious inclusion" of pregnant women in clinical trials.

On April 3, 2018, FDA published long awaited draft guidance entitled "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials." The guidance addresses the scientific and ethical issues of clinical trials that (i) include the enrollment of pregnant women and (ii) allow enrollees who become pregnant to remain in the trial—both in the context of drugs intended to treat pregnancy specific conditions and drugs intended to treat conditions that occur primarily among females of reproductive potential.

The guidance describes the historical exclusion of pregnant women from clinical trials, which has significantly limited information about the effects of common and necessary treatments on pregnant women and their fetuses. To date, information about the effects of drugs taken during pregnancy has been generally collected after a drug's FDA approval and through observational studies such as pregnancy exposure registries, which suffer from over reporting bias and other inherent flaws that limit the usefulness of data provided. FDA strongly assesses this lack of information stating, "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."

The guidance provides FDA's mindset toward rectifying this information gap, some highlights of which include:

> 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.

Distinguishing "Research-Related Risks" from "Independent Risks"

FDA distinguishes "research-related risks" (those specifically associated with clinical trial interventions and procedures) from "independent risks" (those not associated with the clinical trial). For example, a clinical trial that includes pregnant women who had previously been prescribed a drug and is limited to collecting data pertaining to the pregnancy would be considered to pose no "research-related risk" except those associated with study-specific risks, such as a blood sample collection. The FDA would, in contrast, consider risks associated with the previously prescribed drug to be "independent risks".

Potential for Exposing a Fetus to Greater than Minimal Risk

Circumstances may exist in which pregnant women can be enrolled in clinical trials that potentially expose a fetus to a greater than minimal risk if the trial offers the potential for direct clinical benefit to the enrolled pregnant woman and/or her fetus. Examples include:

- A needed, but otherwise unavailable, therapy (e.g., a new antituberculosis drug for multidrug resistant disease).
- A drug or biologic that reduces the risk for either the fetus or pregnant woman to acquire a serious health condition (e.g., a vaginal microbicide that reduces transmission of HIV).

Ethical Justification

FDA considers it ethically justifiable to include pregnant women in clinical trials in the following situations:

- In the postmarketing setting (i.e., FDA-approved drugs), so long as (i) adequate nonclinical studies

have been completed; (ii) 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 (iii) efficacy cannot be extrapolated or safety cannot be assessed by other study methods.

- In the premarketing setting (i.e., investigational drugs), so long as (i) adequate nonclinical studies have been completed; and (ii) the clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available.

Additional Considerations

FDA offers these additional considerations for sponsors and investigators:

- Obtain adequate reproductive and developmental toxicology data in relevant nonclinical models.
- Evaluate the gestational timing of exposure to the investigational drug in relation to fetal development.
- Choose an appropriate control population.
- Use pharmacokinetic data to determine dose or dosing regimen changes between pregnant and nonpregnant women.
- Utilize a planned interim analysis to assess efficacy of the control group versus the pregnant women in determining if and when to stop the clinical trial.
- Consult with bioethicists and FDA when *designing* a clinical trial.

The comment period for the guidance closed on June 8, 2018, and the timing for the issuance of final guidance is unknown.

TWO KEY TAKEAWAYS

1. Including pregnant women in clinical trials is necessary to close the gap in information to allow for informed prescribing decisions during pregnancy.
2. Thoughtful planning and design of clinical trials is key to limiting research-related risks to pregnant women and their fetuses.


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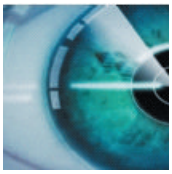
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