Evaluation of Sex Differences in Clinical Investigations

Information Sheet
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Chief Medical Officer
Office of Clinical Policy
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Good Clinical Practice

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Contains Nonbinding Recommendations

Evaluation of Sex Differences in Clinical Investigations Guidance for Industry[1]

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INTRODUCTION

On July 22, 1993, the FDA published a guideline related to the assessment of sex differences in clinical evaluation of drugs amidst growing concerns that the drug development process did not provide adequate information about the effects of drugs or biological products in women and a consensus that women should be allowed to determine for themselves the appropriateness of participating in early clinical trials [58 FR 39406].

Many aspects of the guideline may be important to an Institutional Review Board (IRB) as part of its initial deliberations about protocols and ongoing surveillance of research. While the guideline specifically addresses drug and biologic testing, the Agency suggests that when reviewing medical device studies, IRBs consider whether the principles of the guideline apply to the device under investigation and, if so, whether to include these principles in their review of the protocol. IRBs should be aware that the FDA guideline represents current policy and describes the Agency's expectations regarding the inclusion of participants in 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.

DISCUSSION

The following critical changes from the guideline should be reflected in drug and biologic product protocols presented to IRBs:

- First, the guideline lifts a restriction on participation by most women with childbearing potential from entering Phase 1 and early Phase 2 trials, and now

[1] This guidance has been prepared by the Office of Clinical Policy within the Office of the Chief Medical Officer at the Food and Drug Administration.

encourages their participation. FDA believes that early drug and biologic trials can be safely conducted in women even before completion of all animal reproduction studies through protocol designs that include monitoring for pregnancy as well as measures to prevent pregnancy during exposure to investigational agents. Pregnancy testing is recommended, and women must be counseled about the reliable use of contraception or abstinence from intercourse while participating in the clinical trial. The guideline does not, however, specify the type of contraception to be used because FDA believes that decisions of this nature are best left to the woman in consultation with her health care provider. It is important that investigators have access to gynecologic consultants who can provide information about contraceptives and advice for study participants.

- Second, sponsors should collect sex-related data during research and development and should analyze the data for sex effects in addition to other variables such as age and race. FDA requires sponsors to include a fair representation of both sexes as participants in clinical trials so that clinically significant sex-related differences in response can be detected. The guideline also underscores the importance of collecting pharmacokinetics data on demographic differences beginning in the Phase 1 and 2 studies, so that relevant study designs are developed for later trials.
- In addition, three specific pharmacokinetics issues should be considered when feasible: (1) effect of the stages of the menstrual cycle; (2) effect of exogenous hormonal therapy including oral contraceptives; and (3) effect of the drug or biologic on the pharmacokinetics of oral contraceptives.

Informed Consent Issues

A critical responsibility of the investigator and the IRB has always included ensuring that there is an adequate informed consent process. When preclinical teratology and reproductive toxicology studies are not completed prior to the initial studies in humans, all participants should be informed about lack of full characterization of the test article and the potential effects of the test agent on conception and fetal development. All participants should be provided with new pertinent information arising from preclinical studies as it becomes available, and informed consent documents should be updated when appropriate. Study participants should also be informed about any new clinical data that emerge regarding general safety and effectiveness, including relevant sex effects.

Summary

IRBs now have broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA appreciates the cooperation of IRBs in assisting the Agency to foster changes in product development that will promote the overall health of all people. FDA urges IRBs not to needlessly exclude women or other groups.