

“Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs” (July 1993), by the United States Food and Drug Administration

The US Food and Drug Administration, or FDA, published the “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” henceforth “Study of Gender Differences,” in July 1993. The document defined acceptable practices for investigators studying new drugs. Prior to 1993, investigators excluded most women from clinical trials because in 1977, the FDA recommended that anyone who could possibly become pregnant be excluded from early phase drug research to minimize risk to a potential fetus. In 1997, the FDA reversed that guidance, advising investigators to include women in early phase drug research, a decision that reflected changing views about a woman’s ability to decide whether to participate in drug trials and furthering research on the effects of drugs on women.

In the US, the FDA regulates the safety and efficacy of drugs. To do that, the FDA establishes guidelines for drug manufacturers and publishes recommendations for investigators performing clinical studies. Between 1977 and 1993, investigators excluded women from early phase clinical research to ensure the investigators did not expose any fetuses to untested drugs.

During the early 1990s, people paid increasing attention to women’s health and the inclusion of women in drug trials. The Women’s Health Equity Act proposed in 1990, 1991, and 1993 sought to ensure equal research and attention on men and women’s health. One month before the FDA published “Study of Gender Differences,” the US National Institutes of Health Revitalization Act passed with explicit wording for including women in drug trials. At the same time, the public began to address rising rates of breast cancer and several politically active organizations emerged with the goal of advocating for increased breast cancer research and prevention measures. Those organizations petitioned Congress in 1993 demanding that Bill Clinton, president of the US, establish an action plan to improve breast cancer research, funding, and awareness. The petition received over 2.6 million signatures and Clinton established the National Action Plan on Breast Cancer in 1993.

The FDA separates “Study of Gender Differences” into three general sections. First, they establish that the 1977 guideline was detrimental to women’s health because investigators excluded women from early clinical research and drugs can work differently in men’s and women’s bodies. Then, the FDA provides suggestions about how to address what was wrong with the 1977 guideline. They suggest that investigators should intentionally include women in their research. Finally, they discuss some aspects of the 1977 guideline that they would recommend to maintain, like precautions to prevent investigators from exposing fetuses to untested drugs.

The first section in “Study of Gender Differences” is an introduction and background section in which the FDA outlines their intentions for modifying the 1977 guidelines. They give background on women’s historic lack of participation in drug trials and outline the types of research women are typically involved in. They assert that the reason the FDA published the original 1977 guideline was to prevent investigators from exposing fetuses to untested chemicals. The FDA states that women’s health research is lacking in areas like brain disease, heart disease, the menstrual cycle, and the effects of birth control. In the first section, the FDA also acknowledges concerns that the 1977 guideline was too rigid in its exclusion of women from drug research, stating that it took away

women's agency in making the decision to participate in research. Finally, the FDA describes some areas of research where there are differences between men and women and acknowledges that the guidance in the 1977 document may have prevented that research from occurring. They establish that their position on the inclusion of women in clinical studies does not reflect a lack of concern for possible harm to a fetus but instead prioritizes the agency of investigators, women, and women's doctors in making decisions.

Following the introduction and background, the FDA states that different people react to drugs differently, which means that drug research needs to include different kinds of people. They list age, gender, race, and co-existing illnesses as some of the factors that can make drugs act variably from person to person. The FDA states that people can absorb, metabolize, and excrete the drug differently based on those factors. They discuss some reasons why drugs might work differently between people. One reason the FDA cites is actual differences in the way the body processes the drug, calling them pharmacokinetic differences. Another difference they cite is the social context around which people use the drug. For example, social habits like smoking or alcohol use might influence the way a drug works. The FDA concludes the section by claiming that the documented number of differences between genders is small and that performing a study aimed at determining those differences might be difficult but that including both genders in unrelated studies is a valid way of obtaining similar data. The FDA states that such practices are necessary to improve the quality and quantity of health research.

Next, the FDA describes how clinical drug trials should address the problems in the 1977 guideline. The FDA acknowledges that the restrictions on the inclusion of women in clinical drug trials were imposed by the FDA's own 1977 guidance, but the FDA states specifically that they are eliminating those restrictions with their new guidance. They state that the people who will eventually take the drug are the same people investigators should include in their research and so, investigators should include women in their research. The FDA notes that often individuals are taking other drugs and that investigators should not exclude those people. Instead, investigators should note any instances of drug interactions as patients in non-clinical settings are likely to take other drugs. At the end of the section, the FDA describes how a study evaluating drugs should occur. The FDA states that, unless studies are specifically evaluating gender differences, investigators will probably only note significant differences between genders, which is not necessarily the aim of the studies. The guidelines acknowledge that there are so many variables affecting clinical trials that investigators should study the effects of drugs on different populations because those differences are important for understanding the effectiveness and safety of a drug.

The FDA transitions from discussing gender differences and drug effects to the precautions outlined in the 1977 guideline. In the final section, the FDA establishes that investigators should still be careful when testing drugs on women who could potentially become pregnant. The FDA states that their goal is to ensure that investigators do not expose fetuses to potentially harmful drugs. According to the FDA, investigators should generally perform studies that research how dangerous a drug could be to a fetus before they perform clinical studies on women that may become pregnant. If that study has not been performed before the clinical study, the FDA states that investigators should write that information on the consent forms so that women are aware that researchers do not know the possible effects of the drug on a fetus. The FDA concludes their guidance document by establishing guidelines for investigators performing clinical studies on patients of reproductive age. They recommend that investigators inform participants of risks to their fertility and recommend potential alternative treatments before they participate in the study.

Following the publication of "Study of Gender Differences," it is unclear whether investigators have successfully implemented the FDA's guidelines. The Center for Drug Evaluation and Research, an organization within the FDA, conducted a study between 1995 and 1999 in which it examined new drugs that the FDA approved during that time. According to the Center for Drug Evaluation and Research, the rate at which men and women were participating in clinical drug trials was about the same as the rate at which they were affected by the diseases the drugs were meant to treat. That indicates that investigators were including appropriate ratios of men and women in clinical drug trials to treat the population the drug was intended to treat. However, in 2001, the Government Accountability Office conducted another study which found that the FDA had to withdraw ten drugs

from the drug market because those drugs posed health risks to women specifically. The Government Accountability Office study indicates that investigators had not tested the drugs on women thoroughly enough before those drugs were released to the market. In 2013, the FDA published another study evaluating “Study of Gender Differences” effectiveness and found that most studies did not include women at the same rate that they included men, and that investigators did not explore gender-specific results. According to the FDA, that indicates that investigators were not following the guidelines established by “Study of Gender Differences.”

Sources

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