United States General Accounting Office

GAO

Report to Congressional Requesters

October 1992

WOMEN'S HEALTH

FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing

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GAO

United States
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Human Resources Division

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October 29, 1992

The Honorable Henry A. Waxman
Chairman, Subcommittee on Health
and the Environment
Committee on Energy and Commerce
House of Representatives

The Honorable Patricia Schroeder
Co-Chair, Congressional Caucus
for Women's Issues
House of Representatives

The Honorable Olympia J. Snowe
Co-Chair, Congressional Caucus
for Women's Issues
House of Representatives

Drug therapy is the most common and one of the most important forms of medical treatment used for men and women. Because of physiological differences, however, men and women can respond differently to the same prescription drug. For example, women tend to metabolize some antihypertensive and cardiovascular drugs at a slower rate than men. Also, drug interactions with women's hormones and women's use of oral contraceptives during their childbearing years can cause different responses. Despite evidence of important differences in the way gender can affect drug response, drug manufacturers may not be studying drug test data for possible gender-related differences.

Given the potential for different responses to drugs based on gender, you expressed concern that women could be at risk if the Food and Drug Administration (FDA) approves drugs on the basis of clinical trials[1] in which women were underrepresented. At your request, we examined FDA's policies and the pharmaceutical industry's practices regarding research on women in prescription drug testing.

We reviewed FDA's policy guidance for drug manufacturers and interviewed FDA, National Institutes of Health (NIH), and Institute of Medicine officials; pharmaceutical representatives; and experts in pharmacology. We also performed an extensive literature search on topics related to drug testing and clinical trials (see bibliography). We did not

[1]Clinical drug trials involve testing a new drug in humans to determine whether it has therapeutic benefit in fighting disease.

evaluate the appropriateness of FDA's policy that excludes women of childbearing potential from participating in early clinical drug trials. Further, we did not identify the level of female participation in initial drug testing.

In our examination of drug manufacturers' testing practices in the United States, you asked us to provide information on the prescription drugs FDA approved over a recent 3-1/2-year period. Specifically, we were to determine (1) the representation of women in drug testing, (2) the sufficiency of female participation in drug trials to assess significant gender-related differences, (3) the extent to which trial data were analyzed for differences in response related to gender, and (4) whether studies were conducted to examine drug interaction with the varying hormonal status of women and oral contraceptive use.

Because FDA could not readily identify the level of female participation in trials for the drugs in our study, we surveyed all drug manufacturers that obtained FDA approval of drugs containing new chemical properties from January 1988 to June 1991. The questionnaire sought detailed information on the participation of women in clinical drug trials conducted in the United States. We provided our questionnaire results to FDA. A detailed discussion of our objectives, scope, and methodology is in appendix I. A copy of the survey questionnaire, annotated to show total responses to each question, is in appendix II.

Results in Brief

FDA guidance to drug manufacturers recommends that they test new drugs on representative patient populations. FDA, however, does not define "representative," and manufacturers are not consistent in their application of FDA's guidance. A quarter of the drug manufacturers in an industry survey reported that they do not deliberately recruit representative numbers of women as participants in drug trials. Further, more than half said that FDA asked them to include women in drug trials, but the remainder said they had not been asked.

Women were included in clinical trials for all the drugs in our survey but were generally underrepresented in those trials. Our standard of representativeness is a comparison of the proportion of women among clinical trial participants with the proportion of women among those persons with the disease for which the drug is intended. Using this approach, we determined that for more than 60 percent of the drugs, the representation of women in the test population was less than the

representation of women in the population with the corresponding disease.

Although women may not be proportionately represented in trials for some drugs, there were enough to detect gender-related differences in response for most drugs in our survey. The absolute number of women in clinical drug trials is a key determinate of whether manufacturers can detect significant differences in response that may be related to gender, according to FDA. We observed, however, that while the trials supporting most drugs did include at least 250 women, the minimum number suggested by FDA, for about a third of the drugs, fewer than 250 women were included as trial participants.

Even when enough women are included in drug testing, often trial data are not analyzed to determine if women's responses to a drug differed from those of men. Also, many drug manufacturers do not study whether their drugs specifically interact with the hormones present in women, including hormones commonly found in oral contraceptives. This lack of knowledge about gender-related differences in drug response can create a critical gap in information about how best to tailor drug therapies to women.

Background

An agency within the Department of Health and Human Services, FDA is the nation's oldest consumer-protection agency. It regulates nearly $1 trillion worth of products made available annually to the public by the food, drug, medical device, and cosmetic industries.[2] Pharmaceutical sales represent more than $40 billion of this amount.

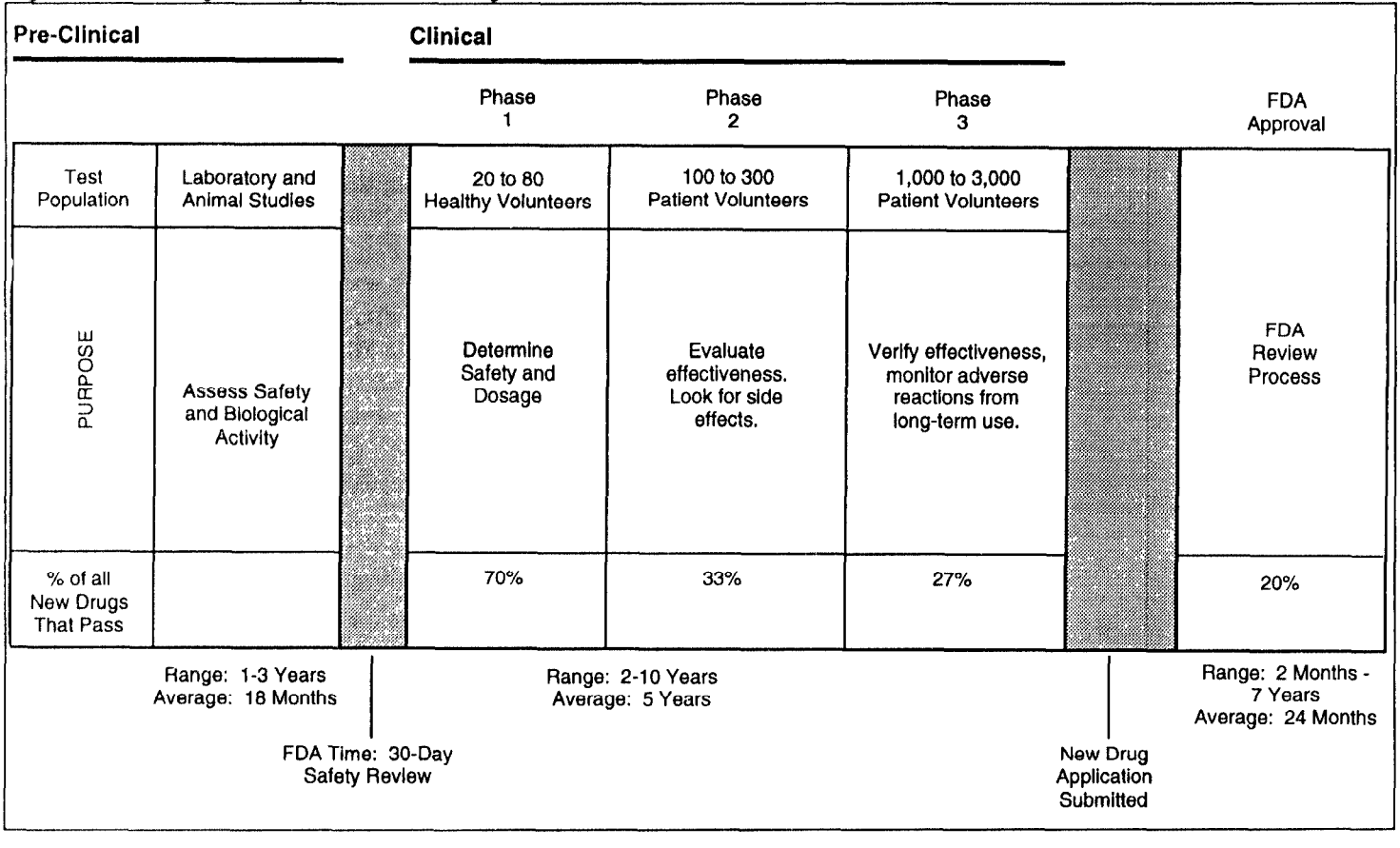
FDA's primary regulatory responsibility regarding pharmaceuticals is to approve new drugs before they are marketed to the public. Annually, FDA approves an average of 20 new prescription drugs. The agency fulfills its drug approval responsibilities by (1) providing guidance for drug manufacturers' use in conducting clinical trials in humans, (2) reviewing manufacturers' proposals for conducting clinical trials to ensure that they are performed in a safe and ethical manner, and (3) evaluating new drugs for which premarket approval is sought to ensure that they are safe and effective. Also, FDA approves new drug labeling. The label indicates the medical conditions and patient populations for which the drug has been tested and approved as safe and effective.

[2]FDA's basic authority is derived from the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.). FDA also has responsibilities under other laws.

Drug Testing and Approval Process

In approving new drugs for marketing, FDA must assure that the public health is protected by carefully assessing the risks and benefits associated with new drugs. Drug manufacturers must demonstrate the safety and efficacy (effectiveness) of new drugs through strict testing before FDA approves them for therapeutic use. After new drugs are tested in the laboratory and on animals and shown to have possible therapeutic benefit, FDA approves them for testing in humans. Clinical trials consist of three phases: Phase 1 is used to determine toxicity and safe dose levels; Phase 2 assesses drug efficacy using small-scale trials; and Phase 3 further evaluates efficacy and monitors adverse responses using large-scale trials. Figure 1 illustrates the new drug development and testing process.

Figure 1: New Drug Development and Testing Process



FDA approves drugs before they are marketed for public use principally based on testing results reported in new drug applications.[3] An application contains, among other things, a summary of the drug's testing history and data from clinical trials, including the distribution of drug trial participants by gender and age. An FDA review team scrutinizes the data from specific technical viewpoints to evaluate the drug's safety and efficacy. In addition to reviews by chemists and pharmacologists, FDA physicians evaluate clinical trial results—including the drug's therapeutic and adverse effects. Statisticians evaluate the designs for each controlled drug trial, the validity of the statistical analyses, and the conclusions of safety and efficacy based on the study data. The review team determines whether the evidence supports the drug manufacturer's claim that the drug is safe and effective under the conditions of use recommended in the proposed labeling.

FDA Policy Excludes Women of Childbearing Potential From Early Trials

One of FDA's policies on clinical drug testing precludes women of childbearing potential from participating in Phase 1 and early Phase 2 trials.[4] This policy was implemented to avoid exposing a fetus to a drug that has not satisfied preliminary safety and efficacy testing. Women of childbearing potential are permitted to participate in trials once evidence of a drug's effectiveness in humans is obtained and data are available from reproductive studies of animals that have examined whether the drug causes birth defects. FDA is reevaluating its policy on the exclusion of women of childbearing potential in the early phases of drug testing. This report does not address the appropriateness of this policy. Nor does the report contain statistics on female representation in Phase 1 drug trials.

Gender-related Differences in Response Exist for Some Drugs

Evidence of the importance of gender-related analyses in drug testing is mounting in health research. For example, with propranolol (a beta blocker commonly used to treat hypertension, abnormal heart rhythms, and angina), men and women tend to respond differently. When men and women ingest identical doses of propranolol, a higher concentration of the drug will remain in the blood levels 8 hours longer in women than in men. Women's physiological differences (body composition, such as smaller

[3]A drug manufacturer must submit a new drug application requesting FDA approval to market a new drug for human use in interstate commerce.

[4]FDA's policy applies only to women of reproductive capability and medicines that are not designed to treat life-threatening illnesses. FDA adopted this policy largely because of an adverse drug experience in Europe during the late 1950s which concerned reports of severe deformities in thousands of babies born to mothers who had taken the drug thalidomide during pregnancy. Following the thalidomide incident, FDA issued guidelines that attempt to protect women and their unborn offspring from the possible harmful effects of new drugs.

size and more fat, and the presence of endogenous [i.e., naturally occurring] sex steroid hormones) and other biological factors (including the presence of exogenous [e.g., ingested] sex steroid hormones) may influence their response to a drug.

Gender-related effects in drug response due to the presence of naturally occurring hormones or use of oral contraceptives have particular relevance for women of childbearing age. Approximately a quarter of all women of childbearing age use oral contraceptives. Drug interactions with oral contraceptives can either decrease the effectiveness of the contraceptives or increase the toxicity of the other drug. For example, many drugs, such as those used to treat epilepsy, sometimes interact with oral contraceptives to make them less effective in preventing pregnancy. Conversely, certain drugs, such as antidepressants, have the opposite effect, interacting with oral contraceptives to increase their potency, sometimes to toxic levels. Likewise, interactions with estrogens, the principal female hormone, may affect drug disposition, thus requiring higher or lower dosages of prescription drugs.

Principal Findings

FDA Guidance Does Not Define Representation of Women in Drug Testing

FDA has not issued specific guidance or criteria for drug manufacturers to use in determining the extent and sufficiency of female representation in Phases 2 and 3 drug trials. The agency's clinical guidance recommends that the full range of those who will be taking the drug after approval be represented in drug testing. However, FDA has not defined the term "representative," nor has it provided guidance to drug manufacturers for determining when sufficient numbers of women are included in clinical trials to detect gender-related differences in drug response. An industry survey[5] showed that drug manufacturers are uncertain as to what FDA expects with regard to including representative numbers of women in clinical trials.

FDA believes that specific guidance for determining the representation of women is not needed because drug manufacturers generally include enough women in their trials. FDA officials base their belief on two surveys conducted in the 1980s on the extent of elderly representation in drug trials. In these surveys, one in 1983 and one in 1989, FDA found that for

[5]Pharmaceutical Manufacturers Association, New Medicines In Development for Women (Washington, D.C., 1991).

most drugs, the representation of women reflected the gender distribution of the incidence of the corresponding disease in women. The agency also believes that the level of female representation was adequate to detect important gender-related differences in drug response.

FDA's belief that specific guidance is not needed for determining the representation of women in drug testing is not reflected in the opinions and actions of the pharmaceutical industry. For example, the Special Populations Committee of the Pharmaceutical Manufacturers Association (PMA)[6] found that the issue of how to best determine what is a representative proportion of women in clinical drug trials is unresolved. A 1991 survey by the committee concluded that there is no consensus on what FDA expects regarding the inclusion of women in drug trials. The survey showed that 56 percent of the major drug manufacturers responded that FDA reviewers had requested that they include women when designing their drug trials, but 44 percent said that the agency had made no such request. Further, 24 percent of drug manufacturers reported that they do not deliberately recruit representative numbers of women as participants in clinical drug trials.[7]

Unlike FDA, NIH, the principal federal agency that sponsors biomedical research, has issued a policy that requires its research project grantees, when designing their studies, to ensure that women are adequately represented. NIH requires that grantees include women in numbers appropriate to the incidence of the disease being studied. The agency is also developing a database to routinely monitor grantees' compliance with this policy.[8]

Drug trials need to include enough women to detect clinically significant differences in response related to gender. However, female participation in

[6]PMA is a scientific and professional trade organization representing more than 100 pharmaceutical firms that discover, develop, and produce most of the prescription drugs used in the United States. The association's Special Populations Committee, composed of 12 clinical doctors from major research-based drug manufacturers, was formed to study the issues involved in testing drugs in special populations, including women.

[7]Some drug manufacturers may be developing drugs that would be used exclusively by men.

[8]Although NIH announced its policy encouraging the inclusion of women in research study populations in 1986 and guidance for implementation was published in 1989, the policy was not applied consistently before 1990. Further, NIH officials had taken little action to encourage researchers to analyze study results by gender. After NIH's implementation of its policy became the subject of congressional hearings in 1990, NIH established the Office of Research on Women's Health to ensure that future NIH-sponsored research appropriately addresses issues relating to women's health and that there is appropriate participation of women in clinical research, especially in clinical trials. See National Institutes of Health: Problems in Implementing Policy on Women in Study Populations (GAO/T-HRD-90-38, June 18, 1990).

the trials for some drugs may not be sufficient to identify such differences. FDA guidelines prescribe a format for presenting demographic characteristics of trial participants and allude to the need for analysis of effectiveness by gender.[9] The guidelines do not, however, provide explicit criteria for determining the level of female participation needed to detect potential differences in drug response. FDA officials believe that usually at least 250 women, regardless of the drug, are needed to detect significant gender-related differences in drug response.

Women Are Not Proportionately Represented in Trials for Some Drugs

Women were included in the clinical trials for all the drugs in our survey, but for about 60 percent of the drugs, women were underrepresented in the trials. Our method of assessing whether women were underrepresented was to compare the proportion of participants in Phase 2 and 3 drug trials conducted in the United States that were women with the proportion of women among those persons with the corresponding disease or condition. This methodology uses the same criterion recommended by NIH and used by FDA in its 1983 and 1989 surveys. The rationale for this methodology is that unbiased random clinical trials should yield a test group that closely approximates the population of patients for whom the drug is intended.

Using this methodology, we rated the participation of women for each class of drugs as comparable, moderate, or low. A clinical pharmacist assisted us in our analysis. As shown in table 1, of the 53 drugs in our survey, 23 percent had a low proportion and 40 percent had a moderate proportion of women.

[9]U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research. Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications, July 1988.

Table 1: Representation of Women in Drug Trials, by Therapeutic Category

		Drugs by female representation rating		
Therapeutic category	**Total drugs**	**Comparable[a]**	**Moderate[b]**	**Low[c]**
Analgesic	4	4	0	0
Anti-infectives	8	3	3	2
Cancer	4	2	1	1
Cardiovasculars	13	1	5	7
Central nervous system	7	4	3	0
Diagnostics	5	2	2	1
Topicals	5	2	2	1
Gastrointestinals	4	1	3	0
Other (hormones, antihistamines, etc.)	3	1	2	0
Total	**53**	**20**	**21**	**12**
Percent	**100%**	**37%**	**40%**	**23%**

[a]Drugs classified as comparable had approximate representational parity, meaning that the representation of women is within plus or minus 10 percentage points of the proportion of patients with the disease who are women.

[b]Moderate representation of women is 11 to 20 percentage points less than the proportion of patients with the disease who are women.

[c]Low representation of women is greater than 20 percentage points less than the proportion of patients with the disease who are women.

The percentage of women included in clinical trials and the representation rating for each drug in our survey are included in appendix III. We also collected, but did not evaluate, data on the level to which women of childbearing age participated in these same drug trials. Appendix IV contains, by drug, the percentages of trial participants that were women of childbearing age.

Low Representation of Women in Cardiovascular Drug Trials

Even though cardiovascular disease is the leading cause of death in women, the representation of women in drug trials was low for half of the cardiovascular drugs in our survey. Table 1 shows that for 7 of the 13 cardiovascular drugs, the representation of women was greater than 20 percentage points less than the proportion of persons with the disease who are women. Women constitute about 50 percent of the patients with heart disease and 58 percent of all hypertensive patients—a risk factor in

heart disease. Other research has also found large gender disparities in cardiovascular drug trials.[10,11]

The low representation of women in trials of cardiovascular drugs is of particular concern because drug companies reported in the PMA survey that they have detected differences in drug response between men and women in this class of drugs. For example, optimal dosages of propranolol, a beta blocker used in the treatment of hypertension, for women may differ from those prescribed for men.

Participation of Women Falls Below Suggested Minimum for Some Drugs

Clinical trials that determine the safety and effectiveness of new drugs need to have a sufficient number of women to detect significant gender-related differences in drug response. Although proportional representation in drug trials is an indicator of the extent of female participation, it is not the key measure of sufficient participation in testing for gender-related drug responses, FDA officials stated. The absolute number of women included in drug trials is the primary factor FDA uses.[12] Using FDA's criterion, we found that a sufficient number of women were included in the U.S. trials for most drugs, but for about one-third of the drugs, there were fewer women than FDA's standard for sufficiency would require.

Although it is not in their official policy guideline, FDA officials gave us specific numbers that they use, as a rule of thumb, to determine whether clinical trials included enough women to detect significant differences in drug response related to gender. FDA officials said that the inclusion of 250 to 1,000 women is usually sufficient to detect important differences in safety and effectiveness between genders. Using this range to measure

[10]Dinah Reitman, a research associate in the Clinical Trials Unit at Mt. Sinai School of Medicine in New York, found that women were underrepresented in drug testing in comparison to their representation in the patient population for the corresponding medical illness in three therapeutic areas: in recent (post-1980) trials of drugs for myocardial infarction, women represented 12 percent of the drug test population but 38 percent of overall heart attack patients; in trials for antiplatelet drugs for preventing stroke, women accounted for 30 percent of the participants but constitute 50 percent of the patients with cardiovascular disease; and in four multicenter trials for antihypertensive drugs involving 21,000 patients, two trials totally excluded women, one had 20 percent female patients, and one had 45 percent. (Discussion of Reitman in C. Hooper, "Some Drug Trials Show Gender Bias," The Journal of NIH Research, Vol. 2, January-February 1990, pp. 47-48.)

[11]Gurwitz and his associates found that almost two-thirds of the clinical studies on heart-attack treatments since 1960 have excluded people over age 75, and only 20 percent of all the patients were women. Because of the exclusion of the elderly—women have heart attack 10 years later than men—studies that excluded older people had proportionally fewer women. Jerry H. Gurwitz, and others, "The Exclusion of the Elderly and Women From Clinical Trials in Acute Myocardial Infarction." The Journal of the American Medical Association, Vol. 268, No. 11 (Sept. 16, 1992), pp. 1417-22.

[12]In reviewing our data, FDA officials maintained that even for the drugs with a "low" representation, there were enough women in the trials to detect important differences in adverse or favorable effects.

adequate participation of women, of the 53 drugs, 17 were below the minimum, as shown in table 2.[13] Five of the drugs that had fewer than 250 women as trial participants were cardiovascular drugs. As previously mentioned, research has found large gender disparities in cardiovascular drug trials.

Table 2: Number of Women in Drug Trials, by Therapeutic Category

		Number of women		
Therapeutic category	**Total drugs**	**More than 1,000**	**250 to 1,000**	**Fewer than 250**
Analgesic	4	2	2	0
Anti-infectives	8	3	3	2
Cancer	4	1	2	1
Cardiovasculars	13	0	8	5
Central nervous system	7	1	5	1
Diagnostics	5	0	2	3
Topicals	5	0	2	3
Gastrointestinals	4	1	2	1
Other (hormones, antihistamines, etc.)	3	0	2	1
Total	**53**	**8**	**28**	**17**
Percent	**100%**	**15%**	**53%**	**32%**

Less Than Half the Drugs Are Analyzed for Gender-related Effects

Even when women were included in drug trials, drug manufacturers did not analyze trial results for most of the drugs in our survey to determine if men and women respond differently to the same drug. Despite evidence that women respond differently to some drugs, of the 53 drugs in our survey, drug manufacturers analyzed 25, or 47 percent, to determine whether men and women respond differently. Further, few drug manufacturers performed studies that focused on gender-specific biological changes in women. For example, only 12 percent of the drugs we surveyed had special studies to examine hormonal interactions or interactions with oral contraceptives in women.

The lack of analysis by gender for the drugs we reviewed may be due partly to the lack of guidelines at the time when the clinical trials were conducted. In 1988, FDA issued guidelines emphasizing the need to analyze trial data by gender and prescribing the format drug manufacturers should use to report data. Many of the drugs in our survey were tested and

[13]For 5 of the 17 drugs, the total number of participants included in the trials conducted in the United States was below 250.

submitted before the issuance of FDA guidelines. However, in its 1992 review of new drug applications pending approval, FDA found that drug manufacturers still are not consistently including analyses of trial data for safety and effectiveness by gender. FDA found that trial data on drug safety was analyzed by gender for only 54 percent of the drugs. Similarly, only 43 percent of the applications contained an analysis of effectiveness by gender. FDA stated that, in complying with its guidelines, drug manufacturers should perform analyses for differences in the safety and effectiveness of new drugs by gender.

Further, FDA officials said that drug manufacturers should examine the role of oral contraceptives and other exogenous sex hormones in drug response in women. Based on the results of their evaluations, drug manufacturers should determine the need for conducting special studies of these factors on a case-by-case basis. FDA guidance does not require that these studies be done.

Conclusions

The representation of women in the clinical trials for some recently approved drugs is low, and data on less than half the drugs were analyzed for gender-related differences in drug response. Even when analyzing the sufficiency of women's participation using the absolute number of women in clinical trials, some drugs fell below the minimum level suggested by FDA. Evidence of important differences in the way men and women respond to the same drug continues to surface. We believe that FDA should ensure that the pharmaceutical industry consistently includes sufficient numbers of women in drug testing to identify gender-related differences in drug response and that such differences are explored and studied.

It is FDA's responsibility to help protect the health and safety of women in the use of prescription drugs by providing appropriate clinical drug trial policy guidance for drug manufacturers to follow in testing new drugs. Although FDA issued guidelines in 1988, drug manufacturers are unclear as to how FDA expects them to determine (1) when there are enough women in a clinical drug trial to detect gender-related differences in drug response and (2) when it is appropriate to study specific physiologically induced drug interactions in women. Further, despite the 1988 guidelines, analyses of the safety and effectiveness of new drugs by gender are often not performed.

Recommendations to the Commissioner of Food and Drugs

To ensure that women are adequately studied in drug trials and that data derived from testing are used to determine whether gender influences drug response, we recommend that the Commissioner issue more explicit policy guidance on the inclusion of women in clinical drug trials. This guidance should tell drug manufacturers how to determine when enough women are included in drug trials to assess potential differences in safety and effectiveness by gender. Additionally, the Commissioner should require that drug manufacturers analyze trial data by gender.

Agency Comments

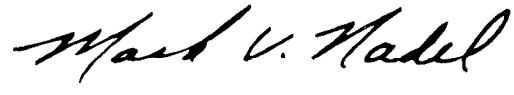
In commenting on a draft of this report, FDA agreed with some findings and disagreed with others. Based on its review of drugs that had low participation of women in trials conducted in the United States, FDA believed that our results supported its previous conclusion that women were adequately represented in drug testing. Moreover, the agency concluded that women under 50 years old (i.e., childbearing age) are as well represented in drug trials as women over 50.

FDA believes that its guidelines for submitting new drug applications are clear in calling for drug manufacturers to analyze trial data on drug effectiveness by gender. However, FDA said that its guidelines are not clear in calling for drug manufacturers to analyze trial data by gender to determine differences between men and women in evaluating the safety of new drugs.

Drug manufacturers examined the interaction of endogenous and exogenous hormones in women for only a few of the new drugs in our survey. FDA agreed that manufacturers should evaluate and, where appropriate, conduct studies to determine drug interaction in women who are taking oral contraceptives and other exogenous sex hormones and that more scientific data are needed on the influence of hormones in drug response.

FDA emphasized that it has been actively involved in reviewing issues relating to the participation of women in drug trials. In June 1992, FDA participated in an Institute of Medicine symposium on women and drug development and in October 1992, cosponsored a symposium on female participation in clinical trials of FDA-regulated products. FDA comments were considered, and we made changes as appropriate.

As we arranged with your offices, we will send copies of this report to appropriate congressional committees and subcommittees, the Secretary of Health and Human Services, the Commissioner of Food and Drugs, and the pharmaceutical firms that participated in our survey. We will also make copies available to other interested parties. If you or your staffs have any questions about this report, please call me on (202) 512-7118. Other major contributors are listed in appendix V.



Mark V. Nadel
Associate Director, National
and Public Health Issues

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Abbreviations

FDA	Food and Drug Administration
NIH	National Institutes of Health
PMA	Pharmaceutical Manufacturers Association

Objectives, Scope, and Methodology

At the request of the Chairman, Subcommittee on Health and the Environment, House Committee on Energy and Commerce, and the Co-Chairs, Congressional Caucus for Women's Issues, we reviewed the policy of the Food and Drug Administration (FDA) and the practices of drug manufacturers regarding the inclusion of women in clinical drug trials. In reviewing pharmaceutical industry practices, we surveyed drug manufacturers to obtain trial data for all new drugs approved by FDA over a 3-1/2-year period and determined (1) the representation of women in drug testing, (2) the sufficiency of female participation in drug trials to assess significant gender-related differences, (3) the extent to which trial data were analyzed for differences in response related to gender, and (4) whether studies were conducted to examine drug interaction with the varying hormonal status of women and oral contraceptive use.

To determine FDA's policy regarding the inclusion of women in drug trials, we interviewed agency officials and reviewed clinical guidance provided to drug manufacturers. We also examined guidelines for the content of new drug applications[1] to determine what specific instructions FDA provides to drug manufacturers for determining (1) the demographic composition and proportional representation of trial participants and (2) the conditions under which analyses of gender-related variables should be conducted.

Questionnaire Survey Methodology

We examined drug manufacturers' practices of including women in clinical drug trials conducted in the United States through a questionnaire sent to drug manufacturers. We surveyed all drug manufacturers that had had a new prescription drug[2] approved by FDA between January 1, 1988, and June 30, 1991. Our questionnaire was developed, with the assistance of FDA officials, to collect data on the characteristics of clinical trial participants and the extent to which drug manufacturers conducted gender-related studies. We pretested the questionnaire with several drug manufacturers and discussed it with the Pharmaceutical Manufacturers Association.

[1]U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research. Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications, July 1988.

[2]We collected data for drugs containing new chemical properties because new molecular drugs are truly novel chemical formulations where inclusion of all segments of the patient population who will ultimately be treated with the drug is most relevant. Further, our survey collected data only for trials performed in the United States. Occasionally, trials are conducted in other countries, and their results are submitted as support for FDA approval of drug manufacturers' new drug applications.

We attained a 92-percent response rate. Sixty-seven questionnaires—one for each new prescription drug—were mailed to 39 drug manufacturers. Based on returned questionnaires and subsequent evaluation, we learned that 4 of the questionnaires were mailed to ineligible recipients (that is, they did not obtain approval to market the new drug indicated in FDA records). Also, 4 questionnaires were eliminated from our analysis because the drugs were intended to treat conditions affecting either men or women exclusively. Of the remaining 59 questionnaires, 5 were not returned and 1 did not contain sufficient data to allow us to analyze the composition of trial participants. We did not independently verify the accuracy of data provided by drug manufacturers. Table I.1 summarizes the questionnaire returns.

Table I.1: Analysis of Questionnaire Returns

	Number
Total questionnaires mailed	**67**
Questionnaires subsequently deleted from the survey:	
Ineligible recipients[a]	4
Ineligible drugs[b]	4
Total drugs surveyed	**59**
Total questionnaires returned	54
Questionnaires not returned	5
Questionnaires returned incomplete	1
Usable questionnaires returned	53

[a]The listing of approved drugs obtained from FDA erroneously included four drugs that were approved for use in clinical trials as having been approved for widespread marketing to the public.

[b]Drugs approved for treatment of medical conditions affecting either men or women exclusively.

Analysis of Data

Our data analysis methodology was designed to (1) evaluate the extent to which female representation in Phase 2 and Phase 3 clinical drug trials conducted in the United States reflected the patient population that will most likely use the drug and (2) determine whether the level of female participation was sufficient to detect significant gender-related differences in drug response. We analyzed the survey responses with the assistance of a clinical pharmacist.

To determine the extent of female representation in clinical drug trials conducted in the United States, we used epidemiological data from Current Estimates from the National Health Interview Survey, 1988

(National Center for Health Statistics, Vital and Health Statistics, October 1989) and other sources to determine the demographics of the medical condition each drug is intended to treat. Using these data, our consultant determined the percentage of people in the United States affected by the corresponding disease or condition who are women. We then compared the percentage of women enrolled in the clinical trial with the percentage of women affected by the corresponding medical condition. The drugs were categorized by therapeutic class, and women's representation was rated as comparable, moderate, or low, in accordance with the parity between the percentage of women exposed to the drug during clinical trials and the percentage of people affected by the corresponding medical condition that the drug is intended to treat who are women.

- Drugs classified as comparable had approximate representational parity; female representation is within plus or minus 10 percentage points of disease proportion.
- Drugs classified as moderate consisted of female representation in the drug trials that was 11 to 20 percentage points less than disease proportion.
- Drugs classified as low consisted of female representation in the drug trials that was greater than 20 percentage points less than disease proportion.

To determine the sufficiency of female participation in Phase 2 and Phase 3 drug trials conducted in the United States, we used FDA's absolute number criterion. FDA officials said that the inclusion of 250 to 1,000 women is usually sufficient to detect important differences in safety and effectiveness of drug response between genders. We compared the number of women enrolled in the clinical trials for each drug with FDA's numbers and determined how many drugs were below, within, and above the range. We did not assess the appropriateness of FDA's criterion.

Except where noted above, our review was conducted in accordance with generally accepted government auditing standards from February 1991 to April 1992. FDA officials commented on a draft of this report, and their comments were incorporated where appropriate.

Annotated Survey Questionnaire

U.S. General Accounting Office

Survey on Characteristics of Subjects in Drug Trials

The United States General Accounting Office (GAO) is conducting a study of the characteristics of human subjects in drug trials to help determine the distribution of drug trial participants by age, gender and race. We are also examining the extent to which testing is done to determine if men and women react differently to the same drug and how these test results are communicated to physicians. We are surveying all drug companies that have obtained FDA approval of a new drug, that is, a new chemical entity, from January 1988 to June 1991. Accordingly, we ask that you complete and return this questionnaire to us in the next three weeks.

If your company tested more than one drug during the period under study, there is a separate section in the questionnaire for each of these drugs. Please complete each section. The label at the beginning of each section identifies each drug for which we want information. Please complete each section.

You may return the questionnaire in the enclosed pre-addressed business reply envelope.

If you have any questions or comments about this survey, please feel free to call Gloria Taylor on (202) 426-1358. In the event that the business reply envelope is misplaced, you may return the questionnaire to:

U.S. General Accounting Office
Attn. Ms. Gloria Taylor
Room 1115
Switzer Building
441 "G" Street
Washington D.C. 20548

The FDA defines phase II clinical drug investigations as controlled clinical trials to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine short-term side effects and risks associated with the drug. FDA defines phase III drug testing as expanded clinical trials with humans to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit/risk relationship of the drug and to provide an adequate basis for physician labeling. Please use these definitions when answering the questions that follow about phase II and phase III testing.

Please answer the following questions about the drug identified on the above label.

1. Please estimate the total number of people in the United States for whom this drug was prescribed in calendar year 1990. (ENTER NUMBER.) (N=47)

   0-3 million people

2. About what percentage of these people were women 15 through 49 years of age, and about what percentage were women of any age? (ENTER THE PERCENTAGE.)[a]

   _____% women 15 - 49

   _____% women of any age

The FDA defines pharmacokinetic differences as differences in the way drugs are absorbed, excreted, metabolized, or distributed. Pharmacodynamic differences are defined by FDA as differences in response to a blood or other tissue concentration of the drug. Please use these definitions when answering questions below about pharmacokinetic and pharmacodynamic differences in both animals and humans.

[a]The number responses was too small to provide meaningful analysis.

Note: N = the number of respondents who answered the question.

NR = no response to the question.

When answering the following questions, please consider only those tests that were conducted in the U.S. for the original new drug application (NDA) to FDA.

The following questions concern drug testing with animals.

3. Were pharmacokinetic or pharmacodynamic tests with animals conducted for this drug that were designed to detect differences between genders? (CHECK ONE.)

   1. [**11**] Yes, pharmacokinetic tests only
   2. [**2**] Yes, pharmacodynamic tests only
   3. [**12**] Yes, both pharmacokinetic and pharmacodynamic tests
   4. [**28**] No (SKIP TO QUESTION 5.)

4. Did your company conclude that any of these tests indicated potentially significant clinical differences between genders? (CHECK ONE.)

   1. [**0**] Yes
   2. [**25**] No

5. At what stage of drug testing were each of the following studies with animals completed for this drug? (CHECK ONE FOR EACH.)

	Before Phase I human clinical trials began	During Phase I	During early Phase II	During late Phase II	During Phase III	Other (SPECIFY.)
	(1)	(2)	(3)	(4)	(5)	(6)
1. Teratology	**21**	**11**	**4**	**6**	**4**	**1**
2. Reproduction	**15**	**7**	**5**	**7**	**8**	**1**
3. Fertility	**16**	**9**	**4**	**5**	**6**	**1**

The following questions concern Phase II and Phase III drug testing with human subjects.

6. Were any phase II human clinical trials conducted for this drug exclusively with male subjects? (CHECK ONE.)

   1. [**14**] Yes

   2. [**38**] No (SKIP TO QUESTION 10.)

      1 NR

7. How many human clinical trials, that is, trials with distinct protocols, were conducted for this drug exclusively with male subjects at phase II of testing? (ENTER NUMBER.) **(N=16)**

   0-24 clinical trials

8. How many male subjects, in total, were actually administered this drug in all of these phase II clinical trials? (ENTER NUMBER.) **(N=14)**

   3-267 male subjects

9. Consider the **males** who were actually administered this drug in all of the **phase II** clinical trials conducted exclusively with males. Enter the number of these male subjects, by age category, who belong to each of the racial/ethnic groups listed below. **(N=14)**

Racial or Ethnic Group	How many males under 15 yrs.? (ENTER NUMBER.)	How many males 15 - 49 yrs.? (ENTER NUMBER.)	How many males 50 - 64 yrs.? (ENTER NUMBER.)	How many males 65 yrs. and over? (ENTER NUMBER.)
1. White (not Hispanic)	**0**	**2-218**	**0-24**	**0-25**
2. Black (not Hispanic)	**0**	**0-85**	**0-17**	**0-8**
3. Hispanic	**0**	**0-8**	**0-1**	**0**
4. Asian/Pacific Islander	**0**	**0-6**	**0**	**0-1**
5. American Indian/ Eskimo/Aleut	**0**	**0-1**	**0**	**0**
6. Other[b] (PLEASE SPECIFY.) _____ _____	**0**	**0-111**	**0-4**	**0-10**

[b]Includes unknowns, not specified.

10. Were any phase III human trials conducted for this drug exclusively with male subjects? (CHECK ONE.)

    1. [7] Yes

    2. [45] No (SKIP TO QUESTION 14.)

       1 **NR**

11. How many human clinical trials, that is, trials with distinct protocols, were conducted for this drug exclusively with male subjects at phase III of testing? (ENTER NUMBER.) (N=7)

    1-7 clinical trials

12. How many male subjects, in total, were actually administered this drug in all of these phase III clinical trials? (ENTER NUMBER.) (N=7)

    12-551 male subjects

13. Consider the **males** who were actually administered this drug in all of the **phase III** clinical trials conducted exclusively with males. Enter the number of these male subjects, by age category, who belong to each of the racial/ethnic groups listed below. (N=7)

Racial or Ethnic Group	How many males under 15 yrs.? (ENTER NUMBER.)	How many males 15 - 49 yrs.? (ENTER NUMBER.)	How many males 50 - 64 yrs.? (ENTER NUMBER.)	How many males 65 yrs. and over (ENTER NUMBER.)
1. White (not Hispanic)	0	6-61	0-42	0-21
2. Black (not Hispanic)	0	0-218	0-9	0-1
3. Hispanic	0	0-3	0-4	0
4. Asian/Pacific Islander	0	0-445	0-31	0
5. American Indian/ Eskimo/Aleut	0	0-1	0	0
6. Other[b] (PLEASE SPECIFY.) _____ _____	0	0-69	0-8	0-2

[b]Includes unknowns, not specified.

14. Were any phase II human trials conducted for this drug exclusively with female subjects? (CHECK ONE.)

    1. [8] Yes

    2. [44] No (SKIP TO QUESTION 18.)

        1 NR

15. How many human clinical trials, that is, trials with distinct protocols, were conducted for this drug exclusively with female subjects at phase II of testing? (ENTER NUMBER.) (N=8)

    1-13 clinical trials

16. How many female subjects, in total, were actually administered this drug in all of these phase II clinical trials? (ENTER NUMBER.) (N=8)

    12-813 female subjects

17. Consider the **females** who were actually administered this drug in all of the **phase II** clinical trials conducted exclusively with females. Enter the number of these female subjects, by age category, who belong to each of the racial/ethnic groups listed below. (N=8)

Racial or Ethnic Group	How many females under 15 yrs.? (ENTER NUMBER.)	How many females 15 - 49 yrs.? (ENTER NUMBER.)	How many females 50 - 64 yrs.? (ENTER NUMBER.)	How many females 65 yrs. and over? (ENTER NUMBER.)
1. White (not Hispanic)	0	7-109	0-1	0
2. Black (not Hispanic)	0	1-156	0-1	0
3. Hispanic	0	0-23	0	0
4. Asian/Pacific Islander	0	0-4	0	0
5. American Indian/ Eskimo/Aleut	0	0-2	0	0
6. Other[b] (PLEASE SPECIFY.) _____ _____	0	0-199	0-437	0-177

[b]Includes unknowns, not specified.

18. Were any phase III human trials conducted for this drug exclusively with female subjects? (CHECK ONE.)

    1. [5] Yes

    2. [47] No (SKIP TO QUESTION 22.)

       1 NR

19. How many human clinical trials, that is, trials with distinct protocols, were conducted for this drug exclusively with female subjects at phase III of testing? (ENTER NUMBER.) (N=5)

    1-15 clinical trials

20. How many female subjects, in total, were actually administered this drug in all of these phase III clinical trials? (ENTER NUMBER.) (N=5)

    20-912 female subjects

21. Consider the **females** who were actually administered this drug in all of the **phase III** clinical trials conducted exclusively with females. Enter the number of these female subjects, by age category, who belong to each of the racial/ethnic groups listed below. (N=5)

Racial or Ethnic Group	How many females under 15 yrs.? (ENTER NUMBER.)	How many females 15 - 49 yrs.? (ENTER NUMBER.)	How many females 50 - 64 yrs.? (ENTER NUMBER.)	How many females 65 yrs. and over? (ENTER NUMBER.)
1. White (not Hispanic)	0	1-547	0-170	0-152
2. Black (not Hispanic)	0	3-257	0-5	0-4
3. Hispanic	0	8-20	0-3	0
4. Asian/Pacific Islander	0	0-1	0-1	0-2
5. American Indian/ Eskimo/Aleut	0	2	0-1	0
6. Other[b] (PLEASE SPECIFY.) _____ _____	0	1-106	0-135	0-37

[b]Includes unknowns, not specified.

22. How many human clinical trials, that is, trials with distinct protocols that were not exclusively with males or females, were conducted for this drug during phase II of testing? (ENTER NUMBER.) **(N=49)**

0-17 clinical trials

23. How many male subjects, in total, and how many female subjects, in total, were actually administered this drug in all of these phase II clinical trials? (ENTER NUMBER.) **(N=46)**

0-750 male subjects

0-618 female subjects

24. Consider the males and females who were actually administered this drug in all of the **phase II** clinical trials conducted for this drug that were not exclusively with males or females. Enter the number of these male subjects, and the number of these female subjects, by age category, who belong to each of the racial/ethnic groups listed below. **(N=46)**

Racial or Ethnic Group	How many males & how many females under 15 yrs.? (ENTER NUMBER.)		How many males & how many females 15 - 49 yrs.? (ENTER NUMBER.)		How many males & how many females 50 - 64 yrs.? (ENTER NUMBER.)		How many males & how many females 65 yrs. and over? (ENTER NUMBER.)	
	Males	Females	Males	Females	Males	Females	Males	Females
1. White (not Hispanic)	**0-99**	**0-79**	**2-315**	**1-319**	**0-394**	**0-96**	**0-188**	**0-84**
2. Black (not Hispanic)	**0-33**	**0-29**	**0-111**	**1-145**	**0-58**	**0-38**	**0-23**	**0-21**
3. Hispanic	**0-7**	**0-5**	**0-42**	**0-21**	**0-22**	**0-16**	**0-4**	**0-2**
4. Asian/ Pacific Islander	**0-1**	**0-1**	**0-10**	**0-8**	**0-4**	**0-4**	**0-3**	**0-2**
5. American Indian/ Eskimo/ Aleut	**0**	**0**	**0-2**	**0-1**	**0-1**	**0-1**	**0-1**	**0**
6. Other[b] (PLEASE SPECIFY.) _____ _____	**0-32**	**0-28**	**0-137**	**0-94**	**0-241**	**0-125**	**0-99**	**0-57**

[b]Includes unknowns, not specified

25. How many human clinical trials, that is, trials with distinct protocols that were not exclusively with males or females, were conducted for this drug during phase III of testing? (ENTER NUMBER.) (N=52)

0-44 clinical trials

26. How many male subjects, in total, and how many female subjects, in total, were actually administered this drug in all of these phase III clinical trials? (ENTER NUMBER.) (N=51)

44-2,237 male subjects

28-2,439 female subjects

27. Consider the males and females who were actually administered this drug in all of the **phase III** clinical trials conducted for this drug that were not exclusively with males or females. Enter the number of these male subjects, and the number of these female subjects, by age category, who belong to each of the racial/ethnic groups listed below. (N=51)

Racial or Ethnic Group	How many males & how many females under 15 yrs.? (ENTER NUMBER.)		How many males & how many females 15 - 49 yrs.? (ENTER NUMBER.)		How many males & how many females 50 - 64 yrs.? (ENTER NUMBER.)		How many males & how many females 65 yrs. and over? (ENTER NUMBER.)	
	Males	Females	Males	Females	Males	Females	Males	Females
1. White (not Hispanic)	0-93	0-110	14-1,397	21-1,701	9-825	6-797	0-797	0-370
2. Black (not Hispanic)	0-82	0-69	1-279	1-375	0-177	0-150	0-45	0-46
3. Hispanic	0-12	0-7	0-142	0-199	0-46	0-32	0-16	0-14
4. Asian/ Pacific Islander	0	0-1	0-414	0-91	0-58	0-35	0-7	0-2
5. American Indian/ Eskimo/ Aleut	0	0	0-5	0-3	0-2	0-3	0-1	0-1
6. Other[b] (PLEASE SPECIFY.) _____ _____	0-5	0-13	0-514	0-186	0-338	0-154	0-159	0-146

[b]Includes unknowns, not specified.

28. Were phase II or phase III data analyzed to determine if the adverse experience profile for this drug differs between men and women? (CHECK ONE.)

    1. [**25**] Yes

    2. [**26**] No

    2 NR

29. Were any studies conducted with this drug to examine hormonal interactions or interactions with oral contraceptives in women. (CHECK ONE.)

    1. [**3**] Yes, hormonal interactions only

    2. [**2**] Yes, interactions with oral contraceptives only

    3. [**0**] Yes, both hormonal interactions and interactions with oral contraceptives

    4. [**47**] No

    1 NR

30. In any phase of testing that included trials of this drug with humans, were each of the following types of analyses or studies conducted to detect differences between genders? (CHECK ONE FOR EACH.)

	Yes (1)	No (2)
1. Specific pharmacokinetic studies	[**4**]	[**46**] **3 NR**
2. Pharmacokinetic screens	[**5**]	[**44**] **4 NR**
3. Specific pharmacodynamic studies	[**4**]	[**46**] **3 NR**
4. Analysis of data from clinical trials with both males and females to detect pharmacodynamic differences between genders	[**14**]	[**36**] **3 NR**

(IF YOU ANSWERED "NO" TO ALL OF THE ABOVE CHOICES, SKIP TO QUESTION 32.)

31. Did your company conclude that any of these tests indicated potentially significant clinical differences between genders? (CHECK ONE.)

    1. [1] Yes--|
       |--->**(SKIP TO QUESTION 33.)**
    2. [17] No---|

32. Has your company informed physicians that these types of studies were not conducted? (CHECK ONE.)

    1. [1] Yes (SKIP TO QUESTION 34.)

    2. [30] No (SKIP TO THE NEXT PAGE.)

33. Has your company communicated the results of any of these studies to physicians? (CHECK ONE.)

    1. [9] Yes

    2. [8] No (SKIP TO THE NEXT PAGE.)

34. Which of the following mechanisms, if any, has your company used to communicate this information to physicians? (CHECK ONE FOR EACH.)

	Yes (1)	No (2)
1. Product labeling	[6]	[2]
2. Advertisements in professional journals	[3]	[3]
3. Publishing scientific articles	[9]	[1]
4. Detailing to affected groups	[3]	[2]
5. Direct mail	[1]	[4]
6. Other ways you communicated information (PLEASE SPECIFY.)	[3]	[1]

_____

_____

Representation of Women in Phases 2 and 3 Drug Trials, by Therapeutic Category

Drug class	Total subjects	Women (All figures are in percent) Phase 2	Phase 3	Phases 2 & 3	Representation rating
Analgesics					
A	1,417	48	61	60	Comparable
B	1,714	a	a	64	Comparable
C	5,395	51	65	65	Comparable
D	1,248	61	65	64	Comparable
Anti-infectives					
A	3,585	54	57	56	Comparable
B	2,769	44	64	62	Comparable
C	1,859	58	62	60	Comparable
D	983	45	24	36	Moderate
E	222	74	30	37	Moderate
F	1,325	38	39	39	Moderate
G	1,319	a	12	11	Low
H	886	a	a	35	Low
Cancer					
A	569	39	36	38	Moderate
B	2,214	68	100	77	Comparable
C	1,038	50	47	48	Comparable
D	939	28	30	29	Low
Cardiovasculars					
A	343	67	70	69	Comparable
B	109	a	a	48	Moderate
C	698	a	a	42	Moderate
D	1,774	a	a	36	Moderate
E	1,915	16	38	37	Moderate
F	2,130	33	32	32	Moderate
G	1,842	17	30	27	Low
H	3,328	23	31	30	Low
I	1,723	38	31	33	Low
J	1,253	23	30	28	Low
K	1,017	17	22	21	Low
L	761	16	24	23	Low
M	884	a	a	15	Low

(continued)

Drug class	Total subjects	Women (All figures are in percent) Phase 2	Phase 3	Phases 2 & 3	Representation rating
Central nervous system					
A	3,826	48	55	54	Comparable
B	696	50	52	52	Comparable
C	581	41	31	37	Moderate
D	1,243	48	51	50	Comparable
E	580	50	55	52	Comparable
F	987	41	34	39	Moderate
G	1,667	70	40	43	Moderate
Diagnostics					
A	160	50	41	43	Comparable
B	1,101	46	43	45	Comparable
C	410	38	44	41	Moderate
D	1,102	26	29	29	Moderate
E	207	30	27	29	Low
Topicals					
A	371	a	a	40	Moderate
B	730	31	51	42	Moderate
C	662	47	46	46	Comparable
D	465	a	a	53	Comparable
E	715	a	a	34	Low
Gastrointestinals					
A	98	a	a	55	Comparable
B	3,854	8	37	35	Moderate
C	1,917	31	51	37	Moderate
D	2,189	19	27	26	Moderate
Other					
A	646	47	47	47	Comparable
B	545	a	a	31	Moderate
C	979	a	a	41	Moderate

Notes:

Drugs classified as comparable had approximate representational parity, meaning that representation of women is within plus or minus 10 percentage points of disease proportion.

Moderate representation of women is 11 to 20 percentage points less than disease proportion.

Low representation of women is greater than 20 percentage points less than disease proportion.

[a]Unknown.

Representation of Women of Childbearing Age in Phases 2 and 3 Drug Trials

Drug class	Total subjects	Women of childbearing age (All figures are in percent) Phase 2	Phase 3	Phases 2 & 3
Analgesics				
A	1,417	43	50	49
B	1,714	a	a	19
C	5,395	40	38	38
D	1,248	55	32	37
Anti-infectives				
A	3,585	47	49	48
B	2,769	16	45	42
C	1,859	37	28	33
D	983	42	11	28
E	222	44	21	24
F	1,325	10	13	12
G	1,319	a	9	8
H	886	a	a	a
Cancer				
A	569	25	22	24
B	2,214	17	18	18
C	1,038	9	9	9
D	939	3	8	6
Cardiovasculars				
A	343	36	36	36
B	109	a	a	25
C	698	a	a	17
D	1,774	a	a	14
E	1,915	6	13	12
F	2,130	11	10	10
G	1,842	8	11	10
H	3,328	7	9	8
I	1,723	8	9	8
J	1,253	10	7	8
K	1,017	3	7	6
L	761	3	6	5
M	884	a	a	1

(continued)

Drug class	Total subjects	Women of childbearing age (All figures are in percent) Phase 2	Phase 3	Phases 2 & 3
Central nervous system				
A	3,826	39	47	47
B	696	43	42	43
C	581	33	28	31
D	1,243	30	26	27
E	580	21	39	26
F	987	28	11	23
G	1,667	60	7	13
Diagnostics				
A	160	38	27	30
B	1,101	18	16	17
C	410	7	17	13
D	1,102	4	13	12
E	207	5	8	6
Topicals				
A	371	a	a	27
B	730	12	37	25
C	662	26	24	25
D	465	a	a	6
E	715	a	a	a
Gastrointestinals				
A	98	a	a	44
B	3,854	6	21	19
C	1,917	16	17	16
D	2,189	8	14	13
Other				
A	646	47	38	39
B	545	a	a	20
C	979	a	a	a

[a]Unknown.

Major Contributors to This Report

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