INCREASING PARTICIPATION OF WOMEN IN EARLY PHASE CLINICAL TRIALS APPROVED BY THE FDA

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Received 13 May 2008; revised 27 September 2008; accepted 28 September 2008

Background. Historically women were excluded from participation in phase 1 clinical trials. The goal of this study was to determine the participation of women and evaluate if participation has increased over time.

Methods. Clinical trial data submitted to the FDA for New Molecular Entities (NMEs) for adult, non-sex specific indications between January 2006 and December 2007 were reviewed. Electronic data available on phase 1 trial were evaluated for proposed indications, sex of participants, and doses tested. Therapeutic doses were obtained from the approved labeling.

Results. FDA approved 34 NMEs in 2006–2007. Data for 352 phase 1 trial of 30 NMEs were obtained. Data for 1 NME was not available electronically, 2 did not include new phase 1 data, and 1 provided only summary demographic data. All NMEs reviewed were for drugs used to treat conditions occurring in both men and women. Overall 120 (34.1%) trials had only male participants while 232 (65.9%) trials also enrolled female participants. 30.6% (3106/10,134) of participants were women. 149/352 (42.3%) of trials included safety and tolerability testing above the highest approved dose. In those trials, 32.5% (1628/5011) of the participants were women. An evaluation of trial start date illustrated the number of trials that enrolled women (p = 0.01) and the number of female participants (p < 0.001) has increased over time.

Conclusion. Females subjects have traditionally been underrepresented in phase 1 trials. The number trials enrolling women and the number of women participating in phase 1 trials has increased since 2001, however, women are still underrepresented.

Introduction

Historically, women have been excluded from participating in Phase I clinical trials. Thalidomide’s teratogenic effects in the 1960s led the US Food and Drug Administration (FDA) to examine the inclusion of females of childbearing potential (FCBP) in clinical trials (Gilbert, 2006). In 1977, the FDA issued the guidance “General Considerations for the Clinical Evaluation of Drugs,” which prohibited the participation of FCBP in Phase I and early Phase II trials (FDA, 1977). FCBP could be included only after results from the preclinical and early Phase II trials showed the effectiveness of a drug in men, older women, or both (Sherman, Temple, & Merkatz, 1995). Although the 1993 Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (FDA, 1993) reversed the 1977 policy, women are not included in early phase trials in sufficient numbers.

A review of the New Molecular Entities (NMEs) approved by the Center for Drug Evaluation and Research (CDER) between 1995 and 1999 was conducted to assess the extent to which women participated in clinical trials for drugs. Data were evaluated for 171 NMEs approved to treat conditions that occur in both men and women. The overall percentages of males and females participating were nearly equal at 51% and 49%, respectively. However, women participated at a numerically lower rate than men in early phase trials. In Phase I and Phase I/II, trials 22% and 25% of subjects were women, respectively (Evelyn et al., 2001). A review of NMEs approved between

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2000 and 2002 found that the percentage of female participants in the clinical trials varied by phase. Women represented only 24% of all participants in the earlier phases (I and I/II), compared with 64% represented by men, and 12% of trials did not specify the sex of participants (Yang et al., in press).

The Government Accountability Office (GAO) completed 2 reports regarding the inclusion of women in clinical trials and FDA regulatory practices. A 1992 GAO report on women’s health concluded women were underrepresented in 60% of clinical trials reviewed and that the FDA needed to do more to ensure the study of sex differences in drug response (GAO, 1992). The most recent GAO report, published in 2001, concluded that, overall, women participated in clinical trials in sufficient numbers to statistically demonstrate whether a drug was effective in women. However, the proportion of women included in different stages of drug development varied greatly. On average women were underrepresented in Phase I trials, representing only 22% of participants in the initial safety trials used to set dosing levels (GAO, 2001b).

The goals of this study were to determine the participation rate of women in Phase I and Phase I/II trials, to evaluate if participation has increased over time, and to determine the dose ranges studied in women.

Methods

We reviewed clinical trial data submitted to the FDA for NMEs between January 2006 and December 2007. Electronic files for Phase I and Phase I/II trials were obtained from the CDER Electronic Document Room. The review was limited to approved drugs used to treat diseases that occur in both men and women. Only trials for adult participants were reviewed. Data from 3 pediatric clinical trials were excluded. Data were abstracted on trial phase, product type, total number of participants, number of male and female participants, and doses tested. Data on approval date and trial start date were recorded. Trials were classified into 2 categories: trials exclusively enrolling male participants and trials that also enrolled females. This second category consisted of trials that enrolled both sexes and trials that exclusively enrolled females. Trial start dates were grouped as 1994 and prior, 1995–1996, 1997–1998, 1999–2000, 2001–2002, 2003–2004, and 2005–2006 to ensure sufficient numbers in each group.

In addition, we examined the FDA Clinical Pharmacology Reviews to determine whether male/female differences were assessed, if differences were noted in drug metabolism between the sexes, and if there were any recommend dose adjustments based on sex. Approved doses were obtained from the drug labeling. The review of the labeling assessed if there were any dose adjustments based on sex or if differences in the efficacy and drug side effects were noted.

Results

The FDA approved 34 NMEs for non–sex-specific indications between January 2006 and December 2007. Data for 352 early phase trials of 30 NMEs were reviewed. Data for 1 NME were not available electronically, 2 did not include new Phase I data in the submissions, and 1 provided only summary data for demographics. Data on trial phase were recorded as specified by the submitting pharmaceutical company, with 349 (99.1%) trials reported as Phase I and 3 (0.9%) trials reported as Phase I/II.

Of the 30 drugs reviewed, 29 (96.7%) enrolled female participants in at least 1 of the Phase I clinical trials. Of the 352 trials, 120 (34.1%) exclusively enrolled male participants; the other 232 (65.9%) also enrolled female participants. Female participation ranged from 3.7% to 100% in the trials enrolling females. Only 2 trials exclusively enrolled females. Of the 352 trials, 149 (42.3%) included safety and tolerability testing above the highest approved dose and 101 (28.8%) of these trials included women. A total of 10,134 participants were enrolled in the trials. Of the 10,134 trial participants, 3,106 (30.6%) were female and 7,028 (69.4%) were male. In the 230 trials that enrolled both sex, there were 7,937 enrolled participants; of these, 3,078 (38.8%) participants were female and 4,859 (61.2%) were male. Of 5,011 participants enrolled in high-dose studies, 1,628 (32.5%) of the participants were women.

Table 1 shows the participation of females in Phase I trials by product type. These data reveal that the number of studies that include female participants is variable, ranging from 100% in reproductive and urologic drugs to 36.4% for neurology products. In product types previously reported to enroll few women, 74.6% of antiviral trials and 54.5% cardio-renal trials included female participants enrolled in Phase I/II trials.

Data were entered into a Microsoft® Excel spreadsheet. Data are presented as numbers and percentages. Using the χ² test for trend, p-values were calculated.

Table 1. Participation of Females in Phase I Trials by Product Type

<table>
<thead>
<tr>
<th>Product type</th>
<th>No. (%) of Studies That Include Female Participants</th>
<th>No. (%) of Studies That Are Female</th>
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</thead>
<tbody>
<tr>
<td>Anesthesia, analgesia, and rheumatology</td>
<td>22 (88.0)</td>
<td>288 (33.8)</td>
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<tr>
<td>Antiviral</td>
<td>50 (74.6)</td>
<td>645 (27.5)</td>
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<tr>
<td>Cardio-renal</td>
<td>30 (54.5)</td>
<td>188 (27.8)</td>
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<tr>
<td>Gastroenterology</td>
<td>6 (60.0)</td>
<td>147 (43.8)</td>
</tr>
<tr>
<td>Metabolism and endocrinology</td>
<td>19 (65.5)</td>
<td>242 (36.4)</td>
</tr>
<tr>
<td>Neurology</td>
<td>12 (36.4)</td>
<td>306 (33.2)</td>
</tr>
<tr>
<td>Oncology</td>
<td>50 (76.9)</td>
<td>747 (34.2)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>19 (67.9)</td>
<td>234 (26.0)</td>
</tr>
<tr>
<td>Pulmonary and allergy</td>
<td>5 (41.7)</td>
<td>43 (24.9)</td>
</tr>
<tr>
<td>Reproductive and urologic</td>
<td>3 (100)</td>
<td>105 (37.2)</td>
</tr>
<tr>
<td>Special pathogen and transplant</td>
<td>16 (57.1)</td>
<td>148 (26.5)</td>
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participants. Cardio-renal and antiviral drugs still have among the lowest percentage of overall female participants at 27.8% and 27.5%. Pulmonary and allergy, psychiatry, and special pathogen and transplant drugs also enrolled <30% female participants, with female participation at 24.9%, 26.0%, and 26.5%, respectively.

Figure 1 shows study balance of Phase I trials by the year the trial began. Percent female participation is categorized as no female participants, 1%–25%, 26%–50%, 51%–75%, 76%–99%, and 100% female participation. An evaluation of trial start date illustrated the number of trials enrolling women has increased over time ($p = .01$). Fewer than 50% of trials that began enrollment before 1999 included female participants. In trials conducted between 1999 and 2000, 53% enrolled women. Of the trials conducted between 2001 and 2006, 70% included female participants. The total number of female trial participants also increased over time (Fig 2; $p < .001$). In trials enrolling before 2001, <25% of participants were women. In more recent times the percentage increased with women representing 32%, 35%, and 30% of early phase trial participants for 2001–2002, 2003–2004, and 2005–2006, respectively.

Of the 30 drugs reviewed, 29 of the FDA Clinical Pharmacology Reviews included an assessment of differences in drug metabolism between the sexes, and recommendation for dosing adjustments based on sex. There were no dose modifications recommended based on sex. One review noted that drug clearance was slightly faster in men, which was incorporated in the labeling. The labeling review found 1 drug with an increased rate of diarrhea at a lower dose in women and 1 drug with a decreased effectiveness in reducing angina frequency in women.

**Discussion**

The improvement in the number of trials that enroll women, as well as an increase in the number of women participating in early phase trials, is encouraging. Phase I trials are the initial introduction of an investigational new drug into humans. Results from Phase I trials are used to assess dose tolerability, assist in establishing the appropriate dose and use of a drug, the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and to gain early evidence on effectiveness. If women do not participate in sufficient numbers in these early trials, dose selection, modifications, or
specific risks or benefits unique to women may not be detected until much later in the drug development process or may go unexplored.

In early phase dose escalation safety and tolerability trials, where drug exposure exceeds the highest therapeutic dose, the importance of including women should be considered because of potential differences in response and because women will be exposed in the postmarketing period. Dose escalation trials at Phase I often include doses above the therapeutic or approved doses, to assess dose tolerability. These trials also determine which investigational drugs are pursued and the doses tested in Phase II trials (FDA, 1998). The inclusion of women at doses above the final recommended dose is important because findings from these trials may have led to a lower recommended dose or identified potential significant adverse events.

The inclusion of women in all phases of drug development is crucial because of the potential for sex-related differences in safety and efficacy. Research has demonstrated sex differences in disease prevalence, severity, and presentation, as well as the response to pharmacologic treatments. There are differences between men and women in drug absorption, metabolism, and elimination. Men and women can respond differently to the same drug or dose (Miller et al., 2001; Wizemann & Pardue, 2001). Hormonal differences can influence the effect of drugs. For example, a woman’s menstrual cycle, pregnancy, or menopause can alter drug metabolism. The use of oral contraceptives or hormone replacement therapy can interact with other drugs (Back & Orme, 1990; Thurmann & Hompesch, 1998). Women are more likely to use multiple medications, including over-the-counter drugs, herbal products, and vitamins (Rademaker, 2001). Studies show women may be at a greater risk of adverse events (GAO, 2001a; Harris, Benet, & Schwartz, 1995). The reasons for this increased risk are not entirely clear, but include sex-related differences in pharmacokinetic, immunologic, and hormonal factors as well as differences in the use of medications by women compared with men (Rademaker, 2001).

Because the drug development period can take an average of 13 years (GAO, 2006), it is important to evaluate enrollment by trial start date. Two drugs approved in the same year may have been studied in different years, under different regulations, different guidelines, and different research environments. Evaluation of participation rates and of factors leading to increased participation must take into account when the trials were conducted, not when the drug was approved.

Multiple reasons for the increased participation of women in Phase I trials may exist. The increase may be due to FDA regulations and guidelines addressing women’s participation in clinical trials and resulting reporting data and analyses by demographic variables including sex, age, and ethnicity. The CDER Manual of Policies and Procedures encourages FDA reviewers to address the inclusion of subpopulations in the reviews of new drugs through the use of standardized review templates (FDA, 2004). The increase may also be due to an increase in public consciousness, the pharmaceutical industry’s increased awareness of the importance of recruiting women, and the implementation of risk management strategies.

Although we are encouraged by women’s increased participation in Phase I trials, there is still room for improvement. The ability to monitor participation during the Investigation New Drug application process, while research is ongoing, will allow protocol or recruitment plan modifications to enroll an adequate number of women in clinical trials and to assess response by sex in early drug development. In addition, more research is needed to identify barriers to women’s participation, identify strategies to encourage participation, and identify ways to increase women’s access to clinical trials.

Conclusion

Although we evaluated drugs used to treat conditions that occur in both males and females, we found that trials are still exclusively conducted on male participants and in the remainder females are underrepresented in Phase I trials. However, our data demonstrate an increased number of Phase I trials enrolled women and increased participation of women in Phase I trials since 2001. Women were also included in clinical trials that included a dose above the highest recommended dose at rates similar to their overall participation at 32.5% and 30.6%, respectively.

References


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