

**Editorial****New Challenges for Statins:  
What the Public Can, or Should, Be Told**

Gender medicine, and some of the most important issues about women's inclusion in clinical trials, has at last been embraced in a big way by the popular press. Front-page news in *The New York Times* and *The Wall Street Journal*: the class action suit against Pfizer Inc. on October 5, 2005, in the US District Court for Massachusetts. It is big news, for several reasons. The suit is being brought on behalf of three parties: a New Jersey Teamsters (Local No. 35) health plan; two plaintiffs (a 73-year-old woman and a 65-year-old man without heart disease or diabetes) representing the allegedly injured groups—women and people age 65 and older; and Health Care For All, a consumer health advocacy group. The accusation? That Pfizer is urging women and patients age 65 and older (as well as the doctors who take care of them) to use atorvastatin (Lipitor®\*) for the primary prevention of coronary artery disease (CAD), although no data demonstrate that the drug will actually do so in these subsets of the population.

Perhaps most important about this historic suit is that 10 years ago, no one would have even conceived of bringing a suit against a pharmaceutical company for asserting that data obtained from men were applicable to women, or that direct testing of females was an unnecessary expense and effort. For decades, academic medicine assumed that men and women were enough alike to hold that what was true of males was also true of females—a colossal intellectual blunder born of expedience. Quite simply, it's cheaper and easier to study men. Certainly it's less risky. The cyclic hormonal variations in premenopausal women plus the hazard of affecting a fetus conceived during the course of a trial were unacceptable obstacles to most researchers within the pharmaceutical industry (represented by the Pharmaceutical Research and Manufacturers of America, PhRMA) and in the academic community. In fact, many have argued that money for research is limited and that requiring investigators to test the impact of biological sex would be an unbearable handicap and actually limit the ability of scientists to expand our fund of knowledge. The objection to powering studies to determine if sex was an important factor in new drug efficacy and/or safety was one I heard personally, over and over again, from both the marketing and scientific sectors of pharmaceutical companies. They openly stated that they didn't want to restrict the potential market for their drug to only half of the population.

The accumulated data from all subspecialties of medicine are now beyond challenge—our knowledge of the significant differences in the normal physiology of men and women and in their experience of the same diseases is expanding exponentially. The more we learn, the more compelling the case becomes for testing new medicines and interventions in both sexes. In 1993, the US Food and Drug Administration (FDA) developed its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs.<sup>1</sup> The FDA expected early gender-specific assessment of safety and efficacy in the course of drug testing; recommended that enrollment in clinical trials be offered to women of childbearing age; and advocated that men should *not* be the sole or primary focus of drug development. On January 18, 1995, in Washington, DC, the Workshop on Gender Guidelines was held to examine what the FDA guidelines meant to pharmaceutical manufacturers and how the latter could ensure the safety of women included in trials.<sup>2</sup> Twenty-five pharmaceutical companies responded to a questionnaire distributed by the workshop organizers before the meeting took place, but only about half of the companies indicated they had a clear understanding of the guidelines. All

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\*Trademark: Pfizer Inc., New York, New York.

agreed, however, that one point was clear: women of childbearing potential (WOCBP), provided they were using birth control, should be included in *all phases* of clinical trials. Furthermore, according to the FDA's mandates, women had to receive "adequate counseling" about possible "toxicity" to their reproductive potential as a condition of participation (drug companies appropriately asked what "adequate counseling" meant to the FDA). To ensure this, early inclusion (in phase 1 trials) of women in the testing process was obligatory unless exclusion was justified "for scientific reasons." "Reproductive toxicology studies" had to be conducted and the results made available to potential trial participants (although it was clear that the data from such studies would not be completed before phase 2 trials began).

About half of the companies had no standard follow-up procedure for an unexpected pregnancy in a trial participant. Understandably, all respondents were concerned about the liability issues connected with such a pregnancy and wanted help in solving the thorny issues involved in this aspect of drug testing in WOCBP. In an effort to address these problems, the workshop participants referred to the National Institutes of Health (NIH) experience with implementing its standards for including women, and WOCBP, in federally funded research. The principle guiding the NIH was that women had to be included in trials unless a scientific rationale existed for excluding them, especially in phase 3 testing. Interestingly, PhRMA representatives believed that internal review boards had often insisted inappropriately on the inclusion of women (including those who were pregnant) in early clinical trials, and the NIH's Office for Protection from Research Risks worked with these boards to decide what exclusion criteria should be used in any given trial of a new drug or intervention. Who should pay for a developmentally disabled child conceived during the course of a clinical trial was not decided, but workshop participants were of the opinion that neither the parents nor the sponsoring drug company should be financially responsible for the care of such an individual: "The costs should

be borne by society, since the outcome of the research will ultimately affect all of society."<sup>2</sup> No machinery for actually implementing such a solution was offered, however.

Merkatz's thoughtful article on the inclusion of women in clinical trials noted that the new policies at the NIH and FDA had resulted in the enrollment of more women in clinical trials and, moreover, in the inclusion of women earlier in the drug development process.<sup>3</sup> She also pointed out something that troubles all of us who are responsible for patients: most drugs taken during pregnancy have not been tested in a pregnant population—and postmarketing surveillance data are probably woefully inadequate as to what is and isn't safe during gestation.

Yet in 1992, the first General Accounting Office (GAO) study on the participation of women in clinical trials found that 25% of drug manufacturers didn't recruit representative numbers of women and that for more than 60% of the drugs tested, the percentage of female participants was less than the percentage of women in the population with the disease. There were, however, *enough data to detect sex-based differences*.<sup>4</sup> A GAO follow-up study of new drug applications from August 1998 through December 2000 reported that pharmaceutical companies were still not presenting the information stipulated by the regulations and that sex-based analysis of the data was still missing.<sup>5</sup>

Another interesting feature of the new lawsuit is its attacks on Pfizer's direct-to-consumer (DTC) advertising of Lipitor, as well as the company's assertions about the drug to health care professionals. Pfizer is accused of urging women and people over the age of 65 to use Lipitor for the primary prevention of CAD although no data prove it would be of benefit. Ad copy is presented in the suit to substantiate the direct targeting of the female patient. As to the value of DTC advertising of medications, a clear consensus from patients or from their doctors has yet to be determined. On one hand, Ahmed and her colleagues lament the "significant under-representation of female patients...in cardiovascular advertisements" and called it gender bias that reinforced the less aggressive treatment of women for car-

diovascular disease compared with men.<sup>6</sup> On the other hand, Mintzes cogently states: “The question is not whether consumers should obtain information about treatment options: the question is whether drug promotion—whose aim is to sell a product—can provide the type of information consumers need.”<sup>7</sup> An editorial in the *New England Journal of Medicine* by Sidney Wolfe<sup>8</sup> seems particularly relevant to this topic and quotes Milton Liebman,<sup>9</sup> writing that “consumers often choose a product on the basis of emotional attributes...How an emotional appeal fits into fair balance in advertising prescription drugs under the requirements and approval process of FDA is not clear.” Despite these uncertainties, drug companies must still believe that DTC advertising is worth the investment—they spent 43% more in the first half of 1999 (\$905 million) than during the same period a year earlier.<sup>10</sup>

In an excellent review by Wilkes et al, the authors noted that in 1981, the pharmaceutical industry argued in a proposal to the FDA that their advertising to the consumer fulfilled an educational purpose.<sup>10</sup> In later arguments to the FDA to liberalize what they might communicate to the patient, PhRMA asked that the lengthy summaries of contraindications, adverse effects, and efficacy demanded by the FDA were expensive, cumbersome, and not suited to electronic media, where 10 to 60 seconds was all that was allotted for an ad. Wilkes and colleagues reviewed the results of a questionnaire they conducted with 329 adults, which found that women were aware of more drug ads than were men, and that awareness was associated with having the disease for which the drug was advertised. Of the respondents, 19% had asked their physicians for specific drugs as a result of reading ads. As for the opinion of health care professionals about DTC advertising, one study by pharmacists found that only 65% of DTC ads presented a fair risk/benefit analysis.<sup>11</sup>

Like hormone therapy was a decade ago, statins are now viewed as the wonder drugs that do everything from quieting inflammation to building stronger bones. They are definitely the darlings of our therapeutic armamentarium.

How much of our enthusiasm is fueled by the commercial goals of the companies that make statins rather than by evidentiary concerns from well-structured studies is impossible to say. Reading the scientific literature critically is not for sissies or the uneducated; it takes time, training, and enormous attention to detail. But most physicians in practice will never read the original studies cited in the brief that accuses Pfizer of inadequate evidence for marketing their bestseller to women and the elderly for the *primary* prevention of CAD. And how do we tell women who have high levels of total and low-density lipoprotein cholesterol that we will give statins only to our dyslipidemic male patients to prevent CAD, if that happens to be the way this issue is resolved? At best, we'll only be able to tell these female patients that data about primary prevention for women don't exist—and may never, by the way. No matter how reassuring the guidelines from the NIH and the FDA are, many women of childbearing age will have powerful reservations about avoiding pregnancy (for fear of harming a developing fetus) for a significant number of years, which would be necessary to make the case for their using statins to prevent CAD. As I have said before, our litigious society often attacks the most valuable individuals and enterprises in our society, and the pharmaceutical industry is one such enterprise.<sup>12</sup>

Very little in medicine is black or white, but this issue is more complex than most. It will be fascinating to read the proceedings of the trial that will follow this brief. It's time all of us studied the implications of DTC advertising, the complexities of assembling a representative population for the proper testing of a new drug, and the skill needed to explore and accurately assess the science behind a therapeutic recommendation. Most troubling of all, how we'll solve the issue of testing the most vulnerable members of our population—even after NIH workshops and a parade of knowledgeable analyses and opinions—remains unknown.

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