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The Disfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap

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The Disfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap

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I. INTRODUCTION

Twice as many women as men receive treatment for clinical depression, yet men benefit more than women from antidepressant drug treat-

ment.¹ Likewise, women use more prescription drugs than men, but suffer proportionally more side effects.² Such disparities stem from the traditional attitude of pharmaceutical companies and researchers toward the use of women in clinical trials.³ In general, researchers have tested drugs on young white males without regard for gender differences,⁴ often assuming that data extrapolated from studies on males are readily applicable to females.⁵ Even medical treatments designed exclusively for women are developed and tested based on a male model, regardless of the fact that women often react differently to many treatments than men do.⁶ Researchers generalize information received from male-oriented studies without sufficient information to show that such treatments will be effective or safe for use by women.⁷ The net result has been the marketing of drugs that are less effective for, and

1. Allen Raskin, *Age-Sex Differences in Response to Antidepressant Drugs*, 159 *J. Nerv. & Ment. Dis.* 120, 120 (1974). In fact, one in five women will suffer serious clinical depression in her lifetime. Elizabeth Sturt, N. Komakura and G. Der, *How Depressing Life Is: Life-long Morbidity Risk for Depressive Disorder in General Populations*, *J. Affective Dis.* 109, 109 (Oct. 1984).

2. These side effects occur even after controlling for the dosage taken. Jean Hamilton and Barbara Parry, *Sex-Related Differences in Clinical Drug Response: Implications for Women's Health*, *J. Am. Med. Women's Ass'n* 126, 129 (Sept./Oct. 1983).

3. "Clinical trials" refers to two different kinds of studies. The first are large scale private clinical intervention trials, used to study effective treatments for health problems such as heart disease. Generally, these large trials are funded by the National Institutes of Health (NIH) subsequent to NIH approval of the study design. The NIH also funds public researchers for studies of various health issues. The second type of clinical trials are used to determine the side effects and efficacy of pharmaceutical products. These trials usually are conducted by private pharmaceutical companies or by private researchers on grants from pharmaceutical houses. These studies must conform to the Food and Drug Administration (FDA) regulations for clinical testing of drugs. Women are systematically excluded from the first type of clinical trials, and women's health issues generally are not addressed in these studies. See Part III.A.

The second form of clinical trials are governed by FDA policies which determine at what point in the clinical trial fertile women can be included. See Part II.A. The net result of the FDA policy is that fertile women often are not the subjects of clinical drug testing before the drugs are released into the market. See Wendy Chavkin and Harold Fox, Letter to the Editor, 264 *JAMA* 973 (1990).

4. Paul Cotton, *Is There Still Too Much Extrapolation From Data on Middle-aged White Men?* 263 *JAMA* 1049, 1049 (1990).

5. Council on Ethical and Judicial Affairs, *Gender Disparities in Clinical Decision Making*, 266 *JAMA* 559, 559 (1991).

6. *Id.* The use of a male model is not unique to the medical profession. As Professor Lucinda M. Finley stated:

[B]ecause pregnancy is in many significant respects different, its similarities to other human conditions can be permanently elusive to legal decisionmakers. Even more problematic for its application to gender issues, however, is the fact that equality analysis is inherently male-biased. The search for sameness is built around male norms, so that what is male is the standard for measurement.

Lucinda M. Finley, *Transcending Equality Theory: A Way Out of the Maternity and the Workplace Debate*, 86 *Colum. L. Rev.* 1118, 1181 (1986).

7. Council on Ethical and Judicial Affairs, 266 *JAMA* at 559 (cited in note 5). See generally Cotton, 263 *JAMA* at 1049 (cited in note 4).

often dangerous to, women.

Researchers and pharmaceutical companies historically have given many reasons for their decision to use a male model in drug development and testing.⁸ Increasingly, however, the medical community, women's health organizations, Congress, and some administrative agencies believe that the exclusion of women from clinical trials is a grave oversight with potentially devastating consequences.⁹ Recently, government agencies and private organizations have taken steps toward encouraging pharmaceutical companies and researchers to include women in clinical trials, but these efforts have had only moderate success.¹⁰ Medical commentators urge that steps must be taken to ensure that the treatment women receive is effective for their physiology.¹¹

Many legal issues surround both the failure to include women in clinical trials and the steps necessary to rectify the consequences of this omission. Either administrative action or traditional litigation could encourage pharmaceutical companies to take women's health care more seriously and, at the very least, to include women in their clinical trials. Government regulation would provide the mandate for researchers and pharmaceutical houses to include women in their trials. Alternatively, the cost of litigation itself might encourage pharmaceutical companies to take such action without government interference.

This Note discusses the history and ramifications of the traditional failure to include women in clinical trials and suggests a variety of means by which pharmaceutical companies could be encouraged to include women in drug testing. Part II examines the reasons behind the traditional exclusion of women from clinical trials, the justifications for continuing that exclusion, and the ramifications of that exclusion for women's health care. Part III addresses the current efforts of the National Institutes of Health, Congress, women's health organizations, and the medical community to encourage pharmaceutical companies and researchers to include women in clinical trials. Part IV discusses some of the legal ramifications of the failure to include women in clinical trials, including the liability of drug manufacturers for the release of drugs not fully tested on women and the Equal Protection Clause issues surrounding the exclusion of women from clinical trials. Part V suggests the means, both legal and economic, by which the inclusion of women in clinical trials could be achieved. This Note concludes that the inclusion of women in clinical trials is necessary for effective health care and

8. See Part II.A.

9. See Part II.B.

10. See Part III.

11. See Council on Ethical and Judicial Affairs, 266 JAMA at 559-562 (cited in note 5).

that the legal community should take steps to encourage pharmaceutical houses to rethink the way they currently test and market their drugs.

II. FROM NONTHINK TO SEXISM—THE HISTORY BEHIND THE DECISION NOT TO USE WOMEN IN CLINICAL TRIALS

A. *The Reasons for the Exclusion of Women from Clinical Trials*

Researchers have given a variety of reasons for the exclusion of women from clinical trials. The cornerstone of these theories is a belief that, for testing purposes, women and men are essentially the same and that any data obtained from the male physiology can be extrapolated to the female.¹² This assumption, although apparently still popular, has attracted severe criticism from the medical community.¹³

Researchers often give a two-fold reason for the exclusion of women that is antithetical to the primary assumption that extrapolation is not only possible but easy. First, women, unlike men, introduce complexities into the research that cause their inclusion in clinical trials to increase the already exorbitant cost of those trials.¹⁴ Second, pharmaceutical houses fear liability for injuries to a woman or her fetus that might occur in a clinical trial.¹⁵

Given the cost of clinical trials, researchers look for a sample population that will present the most homogenous study group. Researchers search for a sample population with the fewest confounding factors,¹⁶ which are thought to increase the complexity of the research.¹⁷ When conducting clinical trials of drugs, researchers characteristically analyze one or more variables while holding others constant. By using uniform subjects, researchers believe they can determine more easily which of the variable effects are caused by the drug itself.¹⁸ Statistically, as the sample population becomes more uniform, the results become more significant in smaller sample sizes, and the research becomes less expensive.¹⁹ The search for homogenous study populations has dominated health care research and often has led to the exclusive study of white

12. *Id.* at 559.

13. See, for example, *id.*; Cotton, 263 JAMA at 1049-50 (cited in note 4); Chavkin and Fox, 264 JAMA at 974 (cited in note 3).

14. Cotton, 263 JAMA at 1049-50 (cited in note 4).

15. See Part IIA. Researchers have traditionally presumed that birth defects are passed through the mother and not the father.

16. Council on Ethical and Judicial Affairs, 266 JAMA at 559 (cited in note 5).

17. *Id.*

18. Lynda Birke, *Women, Feminism and Biology* 57-58 (Methuen, 1986).

19. The more different subgroups are added to a study, the more complex, costly, and time-consuming the study is likely to become.

male subjects²⁰ based on the assumption that they are the most homogenous and readily extrapolated population.²¹ Critics believe that this approach is erroneous since the specificity obtained from a homogenous population ignores the natural complexity of biological events.²²

Researchers generally do not perform studies on sample groups containing only women, although in the name of homogeneity this seems plausible. They claim that it is difficult to control for the hormonal variations prevalent in women and that it would be nearly impossible to design an all-women study that produced clear answers.²³ In other words, female subjects present researchers with several confounding factors, including the menstrual cycle, pregnancy, teratogenic liability²⁴ and menopause.²⁵ Researchers consider these gender differ-

20. Many of the issues surrounding the relative lack of information on women's health issues applies to minority populations as well. Studies have shown differences in the way African-Americans, Asians, Hispanics and the elderly react to drug treatment. Nonetheless, these groups are also traditionally excluded from the clinical trial arena in the quest for a homogenous study sample. See Paul Cotton, *Examples Abound of Gaps in Medical Knowledge Because of Groups Excluded From Scientific Study*, 263 JAMA 1051, 1051 (1990). Although many of the same concerns apply to minority populations, a discussion of those ramifications is beyond the scope of this Note.

21. Dr. Jerry Avorn, a geriatrician and associate professor of social medicine at Harvard University Medical School, has said that this is an assumption made glibly and only because white males run the country. Cotton, 263 JAMA at 1050 (cited in note 4).

Science, although ostensibly neutral and objective, is not always engaged in the disinterested pursuit of truth, but is tied to the values of society at large—values which are male dominated. Birke, *Women, Feminism and Biology* at 8 (cited in note 18).

22. Birke, *Women, Feminism and Biology* at 63.

23. Cotton, 263 JAMA at 1049-50 (discussing the effects of the menstrual cycle on drug treatment).

24. Teratogens (from the Latin word meaning "monster") are agents that produce physical or functional defects in the developing fetus. A teratogenic environment is created when a woman is exposed to teratogens resulting in a birth defect in the fetus or a miscarriage. Edward Saunders and Jeanne Saunders, *Drug Therapy in Pregnancy: The Lessons of Diethylstilbestrol, Thalidomide, and Bendictin*, 11 Health Care for Women Int'l 423, 424 (1990). Teratogenic substances have been linked to embryonic or fetal death, stillbirth, cancer, and immediate or delayed functional birth defects. See Felissa L. Cohen, *Paternal Contributions to Birth Defects*, 21 Nursing Clinics of N. Am. 49 (1986).

Mutagenic substances, on the other hand, are those that cause genetic alterations. Mutations can occur in a number of cells and can result in damage to the parents, immediate offspring, or future generations. Such alterations may or may not manifest themselves in the offspring of those affected because they may be recessive. In order for recessive alterations to manifest themselves both parents must have the mutated gene. Mutations, when manifest, can result in a number of adverse outcomes such as impaired fertility, infertility, spontaneous abortion, congenital abnormalities, birth defects, fetal death and cancer. Id.

There has been a significant amount of disagreement over the precise definition of teratogenicity in both the regulatory and scientific fields. Some researchers include in their definition of teratogens only those substances affecting the fetus from conception to birth. Others include the period after birth, including effects occurring during reproduction and lactation as well. Additionally, researchers are not clear which congenital defects are included as teratogenic effects. Some only include damage to organ development, others include all physical manifestations including central nervous system development defects, while still others include behavioral abnormalities as well. Nanda Gilden and Henk Bodewitz, *Regulating Teratogenicity as a Health Risk*, 32 Soc. Sci.

ences to be methodological problems rather than pertinent factors to be studied.²⁶ They assume that controlling for these factors would be too complex or expensive, so they attempt to account for these differences through extrapolation from males,²⁷ often with disastrous results.²⁸ The notion of confounding factors is so ingrained in the clinical trial arena that researchers even consider female rats too confounding to be included.²⁹

Additionally, the economics of health research financing often prevent studies of women. The United States Department of Health and Human Services through its arm, the National Institutes of Health (NIH), awards large grants for health research and adds to the inequities inherent in clinical research.³⁰ NIH administrators and scientific advisors, most of whom are male, review proposals and assign priority scores that determine the allocation of funding.³¹ These reviewers have enormous discretion in determining who does or does not receive a grant. Furthermore, the reviews determine the study conditions and the

& Med. 1191 (1991). Finally, due to a lack of properly designed studies, researchers often are not certain whether a mutagenic substance will actually manifest in offspring—in other words, the nexus between mutagenic and teratogenic effects of substances is not fully known to researchers. C. A. Schreiner and H. E. Holden, Jr., *Mutagens as Teratogens*, in E. M. Johnson and D. M. Kochhar, eds., *Teratogenesis and Reproductive Toxicology*, 65 Handbook of Experimental Pharmacology, (Springer-Verlag, 1983).

For the purposes of this Note, the term “teratogenic” refers to what Doctors Gilden and Bodewitz refer to as “reproductive toxicity,” which includes all possible effects on the reproductive process including effects on reproductive organs, conception, implantation, and fetal development. Gilden and Bodewitz, 32 Soc. Sci. & Med. at 1193. Additionally, this Note assumes that substances with mutagenic effects have the potential to be teratogenic as well, and are, therefore, substances whose effects researchers wish to avoid.

25. Council on Ethical and Judicial Affairs, 266 JAMA at 559 (cited in note 5).

26. See note 23.

27. See Cotton, 263 JAMA at 1049-1050 (cited in note 4).

28. See Part II.B. Despite whatever concern drug manufacturers and researchers may have for potential liability, drug manufacturers regularly market drugs with insufficient knowledge about their products. The manufacturers do not know if their products will be harmful to women due to the very factors that lead to the exclusion of women in the first place. The damage done by this practice is that the medical profession is not informed about the differences in metabolism and pharmacokinetics with regard to these drugs. Hamilton and Parry, J. Am. Med. Women's Assoc. at 130 (cited in note 2).

29. Hamilton and Parry, J. Am. Med. Women's Ass'n at 130; Joan Hamilton and Peter Hong, *When Medical Research Is for Men Only*, Bus. Week 33 (July 16, 1990).

30. See Mark V. Nadel, *Summary of GAO Testimony by Mark V. Nadel On Problems in Implementing The National Institutes Of Health Policy on Women in Study Populations 2*, 4 GAO/T-HRD-90-38 (U.S. Gen'l Acctg. Office, June 18, 1990).

31. *Id.* at 4. Women's health issues have not fared well in the competition for research dollars. For example, the National Cancer Institute, which has the largest budget of all the NIH departments, spent 10.4% of its \$1.2 billion budget on cancers unique to women. Since there are no breakdowns on funding for men's diseases, such as prostate cancer, it is impossible to determine if the expenditures for women's and men's health care have been equal. *Id.* at 9.

manner in which the studies are conducted.³²

The NIH prioritizes research topics annually, based on political pressure or scientific fashion. The top bureaucrats are men. Only one-third of the proposals approved after scientific review receive funding, and the process of selecting proposals to fund is skewed to the detriment of women.³³ The selection process favors those researchers who have completed many projects successfully in the past.³⁴ The more research a particular investigator has conducted, the higher the priority assigned to that investigator.³⁵ Since women still constitute only a small number of medical researchers, they submit fewer proposals.³⁶ Furthermore, women who are researchers tend to be in the lower echelons of the research hierarchy and, thus, have less extensive track records than most of their male counterparts.³⁷ The low priority given to women's health research may not change until women move into positions of power, for instance as principal investigators of their own research or as members of NIH panels.³⁸

The practice of extrapolating from the male physiology is even more appealing to researchers since the Food and Drug Administration (FDA) has prevented most clinical testing on fertile women unless a substance is first tested either on men or on post-menopausal women.³⁹ Furthermore, because of a desire to protect fertile women from damage to their reproductive health or the health of their future offspring, the FDA does not allow fertile women to be included before the final stages of clinical trials, and then only after full teratogenic studies have been run on animals.⁴⁰ Many in the medical community argue that, since the

32. Id.

33. Id. While the mere fact that funding decisions are made by men does not in and of itself mean that female researchers will get less consideration, a male in charge of the funding decision would naturally give a higher priority to male diseases or diseases affecting both genders than to predominantly female diseases.

34. Women Health Care Consumers: Short Changed on Medical Research and Treatment, Hearing Before the House Subcommittee on Housing and Consumer Interests of the House Select Committee on Aging, 101st Cong., 2d Sess. 80-81 (1990) (statement of Diana Petitti, M.D.).

35. Id. at 80.

36. See note 153.

37. Women Health Care Consumers at 81 (cited in note 34).

38. Cotton, 263 JAMA at 1049 (cited in note 4).

39. Chavkin and Fox, 264 JAMA at 973 (cited in note 3); Food and Drug Administration, U.S. Department of Health, Education, and Welfare, *General Considerations for the Clinical Evaluation of Drugs* 10-11 (Sept. 1977) ("FDA Guidelines").

40. FDA Guidelines (cited in note 39). See also Chavkin and Fox, 264 JAMA at 973 (cited in note 3). For an interesting perspective on gender classifications protective of women, see Sylvia A. Law, *Rethinking Sex and the Constitution*, 132 U. Pa. L. Rev. 955 (1984). Professor Law writes:

First, historically, biology provided a central justification for the subjugation of women. That history partially explains the lack of focus on reproductive difference in contemporary equality doctrine and also suggests the need for close attention to such differences in developing new ideas of equality. Second, "protection" of women—construction of the pedestal/

FDA requires researchers to do all tests on males or infertile females first, it is less costly simply to extrapolate from the data already received than to run teratogenic studies on animals⁴¹ in order to include fertile women in later clinical trials.⁴² According to many in the medical community, this policy has resulted in the categorical exclusion of fertile women from clinical trials of pharmaceutical products.⁴³

As a result of the exclusion of fertile women, drugs are manufactured and marketed for use by those with the very confounding factors deemed unwieldy in clinical trials.⁴⁴ Because they do not study the impact of these drugs on women systematically, researchers see the real differences that exist between men and women only if they stumble upon them later.⁴⁵ Even in studies that include post-menopausal female subjects, researchers seldom delineate differences between the genders.⁴⁶ Since as many differences exist between various age groups of

age—was a core mechanism for oppression of women. Contemporary feminists are hence rightly skeptical of measures that protect women by providing them with special treatment. Id. at 957.

41. Most studies are done on male animals. See text accompanying note 29. Besides the use of only male animals in clinical trials of drugs, behavioral studies also are generally conducted on male animals. For example, the research model for learned helplessness behavior, predominantly a women's problem, was developed from a study conducted on male rats. Hamilton and Hong, *Bus. Week* at 33 (cited in note 29).

42. Chavkin and Fox, 264 *JAMA* at 973-74 (cited in note 3).

43. One spokesman for the FDA, however, denies this allegation, claiming that women, even fertile women, are included in many drug studies and claims to have data to support this view. Telephone interview with Dr. Robert Temple, Director, Office of Drug Evaluation, Food and Drug Administration (January 10, 1992). Dr. Temple cited a recent study of the antidepressant drug Citrolene in which the overall study population included 60% females. During the later phases of the clinical trials, the population of those under 45 years of age was half male and half female, and included fertile women. Fertile women were not included in the early phases of the clinical trials of Citrolene. Id.

Although the main focus of the Citrolene study was age distribution, most respondents also disclosed their gender. Overall, women represented at least 28% of the study population, but how many of those women were fertile is unknown. Robert Temple, *Studies of Older Patients in NDA's for NMEs Approved in 1988*, 4 (Sept. 8, 1989) (unpublished memorandum, on file with the *Vanderbilt Law Review*). The studies cited by the FDA spokesman were designed to measure the number of older people involved in the studies—that the breakdown was also by gender was simply a fortuitous side effect of the studies. Id. Since the studies were broken down by age, the FDA does not know whether the women involved in the studies were pre- or post-menopausal. Id. In order to obtain a clear understanding of the extent of participation of fertile women in clinical trials, the FDA asked the General Accounting Office to make a study of a large number of clinical trials. Id. The information from these studies should be available later this year, but Dr. Temple is fairly certain that the statistics will show that even fertile women are included in clinical trials. Id.

44. Cotton, 263 *JAMA* at 1050 (cited in note 4) (quoting Michelle Harrison, assistant professor of psychiatry at the University of Pittsburgh).

45. Id. (quoting Jean Hamilton, M.D., Director of the Institute for Research on Women's Health, in Washington D.C.).

46. Telephone interview with Dr. Temple (cited in note 43); Hamilton and Parry, *J. Am. Med. Women's Ass'n* at 126 (cited in note 2).

women as between the genders themselves,⁴⁷ the inclusion of older women has done little to resolve the dearth of understanding of women's cycles. As one medical commentator has pointed out, so far researchers have stumbled upon only a tiny fraction of the numerous medical differences between the genders.⁴⁸

B. *The Impact of the Exclusion on Women*

As a result of the traditional notions surrounding women and drug testing, drug manufacturers and researchers have excluded women from many clinical trials in which the need for their inclusion would seem self-evident. For example, researchers recently excluded women from several significant clinical intervention trials on heart disease. Although heart disease is the number one killer of women as well as men,⁴⁹ researchers excluded women because, as a whole, the medical profession views heart disease as a typically male disease.⁵⁰ Furthermore, women are excluded from such studies because, on the average, heart disease strikes them ten years later than it strikes men.⁵¹ In order to study heart disease in women effectively, researchers would need to study experimental female subjects for longer periods of time than male subjects, increasing the cost of the study.⁵²

Despite these problems, some researchers have shown that women's menstrual cycles may be the reason women suffer heart disease later than men.⁵³ These scientists think that the menstrual cycle probably protects women from early heart disease and, therefore, that it may be possible to treat women's heart disease with dosages of estrogen.⁵⁴ Since estrogen once was tried as a treatment for male heart disease with negative results,⁵⁵ researchers have not resumed such treatment for women's

47. Raskin, 159 J. Nerv. & Ment. Dis. at 120-28 (cited in note 1).

48. Cotton, 263 JAMA at 1050 (cited in note 4) (quoting Jean Hamilton). The National Women's Health Network believes that the exclusion of women is an oversimplified method of avoidance with many negative consequences and that the exclusion of women is both ironic and dangerous since women will be using the same products which are too dangerous to be tested on them. National Women's Health Network *Research to Improve Women's Health: An Agenda for Equity* 5 (Dec. 1991) (unpublished position paper, available from the National Women's Health Network, 1325 G St., N.W., Washington, D.C. 20005).

49. Cotton, 263 JAMA at 1051 (cited in note 20).

50. Lawrence Altman, *The Doctor's World: Men, Women and Heart Disease: More Than a Question of Sexism*, N.Y. Times C1, col. 4 (Aug. 6, 1991).

51. Cotton, 263 JAMA at 1051.

52. *Id.*

53. See Altman, *The N.Y. Times* at C1 col. 4 (cited in note 50).

54. *Id.*

55. For example, artificial estrogens, such as DES, were used. While they did decrease the chances for heart disease, they resulted in extreme feminization of the males involved and produced detrimental effects on their reproductive capacity. Roberta Apfel and Susan Fisher, *To Do No Harm: DES and the Dilemmas of Modern Medicine* 19 (Yale, 1984).

heart disease regardless of the indications of possible success.⁵⁶

Similarly, when cholesterol studies emerged linking low density lipid (LDL) cholesterol levels with heart disease, the medical community recommended cutting back on the number of fats and the amount of cholesterol in the diet, and the nation responded. The original studies of cholesterol, however, were performed exclusively on males.⁵⁷ Subsequent studies of women's heart disease suggest that high density lipid (HDL) cholesterol levels, which are also reduced by a low-fat diet, actually can protect premenopausal women from early heart disease.⁵⁸ Thus, women might be at a greater risk by lowering both their LDL and HDL cholesterol levels than they would be by allowing both to remain high.⁵⁹ In addition, the lack of data regarding cholesterol and women's health suggests the need to investigate the effects of oral contraceptives, which potentially can cause excessive amounts of cholesterol in the blood.⁶⁰ No information exists regarding the efficacy of cholesterol lowering drugs when combined with oral contraceptives.⁶¹

The lack of knowledge and research on women's health issues generally has led to two major problems for women's health care. First, doctors and researchers are unaware of many negative side effects unique to women triggered by commonly used prescription drugs. Second, due to the exclusion of women from large studies, many beneficial effects of common drugs are documented for men, while little information exists regarding similar beneficial effects for women.

Although twice the number of women suffer from clinical depression as men, researchers have based the study and the development of antidepressants almost exclusively on a male model.⁶² After drug companies released many antidepressants commonly used for treatment, doctors conducted studies to determine whether age and gender differences existed in response to these drugs.⁶³ These studies revealed that women responded to various drugs differently at different points in the menstrual cycle.⁶⁴ Ironically, the menstrual cycle was the very justification for excluding women from the clinical trials of these drugs in the first place.⁶⁵ The studies showed that some antidepressants had an ex-

56. *Id.*

57. Cotton, 263 JAMA at 1055 (cited in note 20).

58. *Id.*

59. *Id.*

60. The presence of unusually high amounts of cholesterol in the blood is known as hypercholesterolemia. *Tabers Cyclopedic Medical Dictionary* 860 (F. A. Davis, 16th ed. 1989).

61. Cotton, 263 JAMA at 1055 (cited in note 20).

62. Hamilton and Parry, *J. Am. Med. Women's Ass'n* at 130 (cited in note 2).

63. Raskin, 159 *J. Nerv. & Ment. Dis.* at 120-130 (cited in note 1).

64. *Id.*

65. Council on Ethical and Judicial Affairs, 266 JAMA at 559 (cited in note 5).

tremely negative psychological impact on some women during certain points of their menstrual cycle, causing them to become depressive at one point and violent at another.⁶⁶ Drugs designed to produce a euphoric effect were successful in males, but tended to cause females to become violent and hostile.⁶⁷ Due to premenstrual exacerbations of depression, a uniform dose over the entire menstrual cycle may be too high during the first part of the cycle and too low later in the cycle.⁶⁸ This example of pharmacokinetic variation⁶⁹ during menstruation illustrates the lack of clinical understanding of women's cycles.⁷⁰ Most doctors must come to these conclusions on their own since they are rarely included in the literature on pharmaceutical products.⁷¹

Women also suffer proportionately more negative side effects than men, even though men often will have more drug accumulation.⁷² As two clinical psychiatrists have observed, researchers often will use an inappropriately small sample size, one which either does not include women or does not separate data by gender, in determining reactions to various drugs.⁷³ Thus, there is a tendency to conclude that no sex differences exist, a danger made more apparent by the failure to take possible menstrual-related effects into account.⁷⁴

When studies show that drugs have beneficial effects on men, the lack of knowledge concerning the female physiology leads to uncertainty as to whether there will be similar beneficial effects on women. The primary example of this sort of uncertainty is the massive aspirin study conducted in 1981, which used 22,000 male physicians as test subjects.⁷⁵ The results of the aspirin study showed that men can reduce their risk of heart disease if they take aspirin every other day.⁷⁶ According to the study, the effects of a similar dose of aspirin for women were inconclusive.⁷⁷ Stating that the study was inconclusive as to the effects

66. Raskin, 159 *J. Nerv. & Ment. Dis.* at 120-130 (cited in note 1).

67. *Id.*

68. Cotton, 263 *JAMA* at 1051 (cited in note 20).

69. Pharmacokinetics refers to the action of drugs in the body.

70. Cotton, 263 *JAMA* at 1051 (cited in note 20). According to Michelle Harrison, M.D., assistant professor of psychiatry at the University of Pittsburgh, doctors do not know if drugs are being metabolized differently or whether women innately need a higher dosage at different times in their cycle. *Id.* Margaret Jensvold, M.D., in private practice in Bethesda, Maryland, noted that findings regarding the dosage levels in women's menstrual cycles rarely are made in the literature, although physicians often come to the same conclusions on their own through trial and error. *Id.*

71. *Id.*

72. Hamilton and Parry, *J. Am. Med. Women's Ass'n* at 128 (cited in note 2).

73. *Id.* at 130.

74. *Id.*

75. Hamilton and Hong, *Bus. Week* at 33 (1990) (cited in note 29).

76. *Id.*

77. Peter L. Frommer, M.D., Deputy Director of the National Heart, Lung, and Blood Institute in Bethesda, Maryland, contended that even had women been included, the Institute "would

on women suggests that the data on women was difficult to interpret, but in fact the study was inconclusive for women because women were not studied at all.⁷⁸ Researchers presumed not only that there were not enough female physicians to make an effective study, but that female physicians would not have wanted to undergo the inconvenience of taking a placebo.⁷⁹ Doctors attempted to extrapolate from the aspirin data on men, but ultimately were unable to do so safely since aspirin also produced many negative side effects in women.⁸⁰

Years later, researchers determined that aspirin also might have a beneficial effect for women and ran a nonclinical, observational trial on several thousand nurses.⁸¹ The study revealed that aspirin did indeed have beneficial effects for women.⁸² However, because the study was observational, not clinical, its validity is questionable.⁸³ Since that time, the effect of aspirin on women's heart disease, as well as the beneficial effects of drugs on other diseases that affect women significantly, have not been studied with the same intensity as the traditional male diseases.⁸⁴

The concern of FDA regulators and clinical researchers that drugs might have teratogenic effects stems from the most striking example of teratogenic liability in this country—the diethylstilbestrol (DES) crisis. DES was first prescribed in America in 1943, but its efficacy was challenged as early as 1953.⁸⁵ In 1971, the FDA banned the use of DES during pregnancy as a result of DES's carcinogenic properties in the offspring of DES mothers.⁸⁶ DES use became common shortly after

have ended up shrugging [its] shoulders," because the number of female physicians is much smaller and a smaller number would have heart attacks. Cotton, 263 JAMA at 1055 (cited in note 20).

78. Hamilton and Hong, Bus. at 33 (cited in note 29).

79. Cotton, 263 JAMA at 1055 (reporting the comments of Peter Frommer, M.D.) (cited in note 20). Why female physicians would be less willing to inconvenience themselves is not clear. Additionally, the logic behind excluding women because there were not enough female physicians to make an effective study does not hold up since similar research was later conducted on nurses.

80. Id.

81. Lawrence Appel and Trudy Bush, *Preventing Heart Disease in Women: Another Role for Aspirin*, 266 JAMA 565 (1991).

82. Id.

83. Id. Observational studies are based on observation and on data given to the researcher by the subjects in the experiment. Since such studies are not conducted in a clinical setting, it is possible that a variable other than the one being studied is the cause of the change. In order to be absolutely certain of the potential beneficial effects of aspirin in women, a randomized, controlled clinical trial is necessary. Id.

84. National Women's Health Network at 3 (cited in note 48). The Network argues that the male dominated nature of scientific research is the reason women's health issues have received short shrift.

85. Saunders and Saunders, 11 Health Care for Women Int'l at 424-25 (cited in note 24).

86. Id.

World War II, when one in every four pregnancies was unsuccessful.⁸⁷ DES was used to prevent spontaneous abortions, miscarriages, and premature birth.⁸⁸ Initially DES was prescribed only for women with at least one prior unsuccessful pregnancy, but it later became a common prescription drug for any woman thought to be at risk of miscarriage. An estimated three million women eventually were treated with it.⁸⁹ The offspring of DES mothers felt the adverse consequences of DES, mostly in the form of birth defects and cancer.⁹⁰ As a result of the DES crisis, the FDA almost immediately tightened its standards for drug testing, requiring among other things that a drug be efficacious for the purpose for which it is used.⁹¹

The results of DES use were tragic and devastating for the women involved. There is no guarantee, however, that the DES crisis will not be repeated.⁹² It was not tested on animals for teratogenic potential, nor were dose-ranging studies⁹³ run to determine safe dosages or side effects. Probably in response to the DES crisis, the FDA implemented regulations making it very difficult to test drugs on fertile women. Fertile women can be tested only after the dose-ranging and efficacy studies have been completed and only after teratogenic animal studies have been run.⁹⁴ As a result of the additional costs inherent in compliance with these rules, drug manufacturers choose to release many drugs without testing them on women and with no knowledge of their possible teratogenic effects. Currently the best advice the medical community can give to women is to avoid all drugs during pregnancy unless not taking them would put the fetus at greater risk than taking them.⁹⁵

87. Id. at 424.

88. Apfel and Fisher at 26 (cited in note 55) (reprinting an ad for DES appearing in a medical journal and making these claims).

89. Saunders and Saunders, 11 *Health Care for Women Int'l* at 425 (cited in note 24).

90. In the female offspring of DES mothers, a rare form of vaginal and uterine cancer, clear cell adenocarcinoma, developed; structural defects of the cervix, vagina, uterus, and fallopian tubes were discovered; adenosis and dysplasia of the cervix, infertility, adverse pregnancy outcomes such as spontaneous abortions, ectopic pregnancies, premature deliveries, and perinatal deaths have occurred. Also, there is evidence to show that male offspring of DES mothers are more likely to be at risk of anatomic abnormalities of the penis and testes and at an increased risk for reproductive dysfunctions. Id.

91. Id. at 429. Such a regulation would have prevented the marketing of DES.

92. Id. at 430.

93. Dose-ranging studies are used to determine the efficacy and safe dosage levels of drugs. The tests are run on large laboratory animals, such as monkeys or dogs, to determine the margin of safety—the difference between a lethal dose and no effect at all. The first phase of clinical trials on human beings is used to determine a safe dosage range as well as any negative side effect. Richard Ausness, *Unavoidably Unsafe Products and Strict Products Liability: What Liability Rule Should be Applied to the Sellers of Pharmaceutical Products?* 78 *Ky. L. J.* 705, 731 n.166 (1989-90).

94. FDA Guidelines at 10-11 (cited in note 39).

95. Saunders and Saunders, 11 *Health Care for Women Int'l* at 430 (cited in note 24). Saun-

III. CURRENT EFFORTS TO RECTIFY THE KNOWLEDGE GAP

A. *The NIH's Policy to Encourage the Inclusion of Women*

According to many in the medical profession, the quest for a homogenous study population has created a myopic view of clinical research.⁹⁶ This view continues to prevent medical research from being truly effective for the majority of the population.⁹⁷ In order to address this problem, the Public Health Service (PHS), an arm of the Department of Health and Human Services, created a task force to investigate the inequities in women's health care research.⁹⁸ The PHS task force issued a report which listed five criteria to determine whether a particular disease was a women's disease: first, the condition must be unique to women or some subgroup of women; second, it must be more prevalent in women or some subgroup of women than in men; third, it must be more serious in women or some subgroup of women than in men; fourth, the condition must be one for which risk factors are different for women or some subgroup of women than for men; or fifth, it must be one for which treatment interventions are different for women or some subgroup of women than for men.⁹⁹ If any of the criteria are met, then the disease is considered an important women's health issue, and these five criteria remain the current definition for women's health issues.¹⁰⁰

Once a women's health issue was targeted, the PHS report made two recommendations for improved research. First, researchers should expand biomedical and behavioral research to assure emphasis on conditions and diseases prevalent in women of all age groups.¹⁰¹ Second, researchers must make a systematic effort to address the issues relating

ders and Saunders specifically recommend:

(1) No drugs should be taken by a pregnant woman or lactating mother unless specifically approved by her obstetrician-gynecologist or her infant's pediatrician. (2) If drugs are required for a certain condition, the safest drugs at the lowest effective dose should be used. (3) Although it is best to use no drugs during pregnancy, there are a number of medical conditions—like diabetes—that, if left untreated, can put the fetus in considerable jeopardy. In these instances, the risks of the diseases are greater to the fetus than the risks of the drugs required to treat them. . . . (4) Assume nothing, ask questions, and be honest with yourself and your physician. This guideline strongly encourages women to assume an active role in their care.

Id.

96. Cotton, 263 JAMA at 1049 (cited in note 4).

97. In 1989, women constituted 51.2% of the population. The entire population of the United States was estimated at 248,762,000 of which 127,317,000 were women. Bureau of the Census, U.S. Dep't of Commerce 13, *Statistical Abstract of the United States 1991* (11th ed. 1991).

98. See Nadel, *Summary of GAO Testimony* at 1 (cited in note 30).

99. National Womens Health Network at 11 (cited in note 48) (citation omitted).

100. Id.

101. Id.

to gender bias in research.¹⁰²

The Public Health Service agencies, with the exception of the NIH, have largely ignored these recommendations.¹⁰³ The NIH, however, did establish the Women's Health Advisory Committee (the Advisory Committee) to make suggestions on possible ways to implement the PHS report's recommendations.¹⁰⁴ The Advisory Committee made a policy recommendation that the NIH adopted in 1986, urging applicants to include women in any clinical test for which they wanted NIH funding.¹⁰⁵ The new policy further requested that researchers who do not include women give reasons for their exclusion.¹⁰⁶ Additionally, the NIH's policy requested that researchers evaluate gender differences specifically in their findings.¹⁰⁷

Although the NIH instituted its policy with the hope that it naturally would lead to the inclusion of women in clinical trials, the NIH did little to enforce the policy.¹⁰⁸ In fact, the NIH did not publish guidelines for implementing the program until 1989.¹⁰⁹ It is not clear whether the policy has been even moderately successful in accomplishing its stated goal.

In 1989, the Congressional Caucus on Women's Issues asked the General Accounting Office (GAO) to verify whether NIH grant applicants were adhering to the NIH policy.¹¹⁰ Specifically, the Caucus wanted to know whether the NIH had denied any grant applications on the basis that the study population did not include women, or in the alternative, whether the NIH had granted any waivers.¹¹¹ When it filed its report the next year, the GAO determined that the NIH had made little progress in implementing its policy.¹¹²

The GAO found three reasons for this lack of success. First, the policy had not been communicated within the NIH itself and had been applied inconsistently among the institutes.¹¹³ The policy was not used

102. Id. at 11-12.

103. Id.

104. Nadel, *Summary of GAO Testimony* at 3 (cited in note 30).

105. Id.

106. Id.

107. Id. The report concluded that 13.5% of the NIH budget had been spent for women's health issues but rather contended that this did not mean that the remainder of the money was spent on men's diseases. The NIH stated that the majority of funds was spent for the study of diseases that affect both genders. *Women Health Care Consumers* at 84 (cited in note 34) (statement of William F. Raub, Ph.D., Acting Director of the NIH).

108. Nadel, *Summary of GAO Testimony* at 3.

109. Id.

110. Cotton, 263 *JAMA* at 1050 (cited in note 4).

111. Id.

112. See Nadel, *Summary of GAO Testimony* at 90-38.

113. Id.

by some institutes in reviewing research applications until 1991, one year after the GAO report.¹¹⁴ The GAO found that the NIH had actually undermined its own policy by not considering the inclusion of women as a key factor in determining the scientific merit of a proposed study.¹¹⁵ The Division of Research Grants, which is responsible for reviewing upcoming grant applications, had directed its reviewers not to consider compliance with the NIH policy until the scientific merit of the study had been assessed.¹¹⁶ The GAO stated that the failure to consider the study population as a factor in determining scientific merit downgraded the importance of the policy.¹¹⁷

Second, the NIH had taken no action to assist or encourage researchers to analyze conclusions by gender.¹¹⁸ To the extent the policy was implemented, it dealt entirely with ending the exclusion of women from study populations, but did not focus on whether diseases and treatments affect men and women differently.¹¹⁹ Third, the NIH could not demonstrate the policy's effect since no readily accessible source of data on the demographics of NIH study populations exists. Therefore, an evaluation of the policy's effect on studies completed after 1987 is impossible, and the NIH was unable to provide the GAO with information on previously funded all-male studies.¹²⁰ Finally, the NIH applied its policy only to outside studies, not to studies actually conducted by the NIH institutes.¹²¹

The GAO recommended that the NIH inform both its staff and the researchers who receive NIH funding of the reasons for the policy.¹²² The GAO stated that the NIH grant applications should be revised to include the policy and instructions requiring applicants either to include women or to justify their exclusion.¹²³ The GAO also recommended that the NIH instruct scientific review groups to determine whether the gender of the study population is scientifically relevant.¹²⁴ The NIH then would maintain this data in some readily accessible form.¹²⁵ In spite of the GAO's report, the deputy director for the NIH's National Heart, Lung, and Blood Institute, which funded the large

114. *Id.* at 5 (cited in note 30).

115. *Id.* at 9.

116. *Id.*

117. *Id.*

118. *Id.* at 11.

119. *Id.*

120. *Id.* at 11-12.

121. *Id.* at 10.

122. *Id.* at 12.

123. *Id.* at 13.

124. *Id.*

125. *Id.* at 12.

clinical intervention trials on heart disease from which women were excluded, challenged those who question the policy's effectiveness to demonstrate how the NIH has been derelict.¹²⁶

The NIH did take steps in response to the GAO report. In 1990, the NIH established the position of Associate Director for Research on Women's Health and authorized it to monitor the institutes of the NIH.¹²⁷ The NIH also altered its policy to include a mandate that researchers either include women in clinical research or justify their exclusion.¹²⁸ Despite the flurry of activity that has occurred in the wake of the GAO report, the NIH's enforcement of the policy has continued to be lax and only recently has Bernadine Healy, the current director of the NIH, begun to enforce the policy.¹²⁹

The NIH's failure actively to enforce its policy parallels the attitude adopted by the FDA. Both entities seem to think that pharmaceutical companies will do voluntarily what is necessary to ensure that their products are suited for various subgroups.¹³⁰ Thus, both agencies may think that they do not need to take a more active role.¹³¹ Furthermore, since NIH grants affect only those who do not receive funding from private pharmaceutical houses, some have questioned the extent to which NIH policies actually have changed the way large pharmaceutical houses do business.¹³²

B. Congress's Initial Efforts to Rectify the Exclusion

Congress also has attempted to rectify the knowledge gap concerning women through legislation. In 1989 the Congressional Caucus for Women's Issues developed a set of bills called the Women's Health Equity Act of 1990.¹³³ In 1991 the House of Representatives passed the bill, which would create an Office of Research on Women's Health.¹³⁴ The House designed the Office to address women's health issues and to rectify the differential treatment given women in many areas of the

126. Cotton, 263 JAMA at 1050 (cited in note 4) (reporting statements by Peter L. Frommer, Deputy Director of the National Heart, Lung and Blood Institute).

127. Women Health Care Consumers at 105-06 (cited in note 34) (letter of Ruth Kirschstein, M.D., Acting Associate Director on Women's Health at NIH).

128. *Id.* at 105.

129. See Bernadine Healy, *Women's Health, Public Welfare*, 266 JAMA 566 (1991).

130. Cotton, 263 JAMA at 1049 (quoting FDA spokesman Mike Shaffer).

131. But see Healy, 266 JAMA at 566 (cited in note 129).

132. *Id.* An industry spokesman, Lionel Edwards, M.D., chair of the Pharmaceutical Manufacturers Association's new Special Populations Committee, noted that studies could be "subgrouped to death." *Id.* More than 50% of the population is a large subgroup to ignore, however.

133. The Act was resubmitted as the Woman's Health Equity Act of 1991 for the 1991-92 congressional session, S.514, 102d Cong., 1st Sess. (1991).

134. National Institutes of Health Revitalization Amendments of 1991, H.R. 2507, 102d Cong., 1st Sess. § 141 (July 25, 1991), in 137 Cong. Rec. H.5848.

medical profession.¹³⁵

In order to accomplish this goal, the director of the Office would identify projects of importance to women's health that the NIH should fund.¹³⁶ The director also would make recommendations on the best agenda for supporting such projects¹³⁷ and promote the proper allocation of resources to such projects.¹³⁸ In addition, the Office would take active steps to insure the inclusion of women in clinical research.¹³⁹

The House included some parts of the Women's Health Equity Act in its NIH revitalization amendments with the express intent of addressing issues surrounding women's health care.¹⁴⁰ The Senate's version of the Women's Health Equity Act contains many of the same elements as the House bill, although it has yet to come to a full vote before the Senate.¹⁴¹ The purpose of both the Senate and House versions is to insure that women's health issues, such as breast cancer, which affect a large and growing number of women annually are not left unaddressed by the medical and research communities.¹⁴² The Women's Health Network hopes that Congress will pass this legislation, since it would be a major step forward for women's health research.¹⁴³

Despite these halting steps taken by Congress, many in the medical community believe that if anything is to be done about the failure to include women in clinical trials, it will have to be done by women.¹⁴⁴ Commentators recognize that the odds are against those who wish to fill these gaps in clinical research data.¹⁴⁵ Only seven years after its adoption, the FDA's policy of including the elderly has stagnated,¹⁴⁶ and

135. *Id.*

136. *Id.*

137. *Id.*

138. *Id.*

139. *Id.*

140. *Id.* The bill also would create an Office of Research on Women's Health to address the mental health and substance abuse concerns of women. *Id.* § 142, in 137 Cong. Rec. H5849. Additionally, the bill would authorize a \$50 million grant specifically for breast cancer research. *Id.* § 501, in 137 Cong. Rec. H5855. The bill would provide for \$5 million for the development and operation of fertility research centers and protocols for training physicians, scientists, nurses and other health professionals. *Id.* §§ 901, 902, in 137 Cong. Rec. H5856. This portion of the bill was included in the House and Senate NIH reauthorization bills, although the language was taken out of the Senate bill prior to passage. The bill also would authorize and fund projects on women and AIDS research, *Id.* tit. XV, in 137 Cong. Rec. H5860, and other important women's health issues.

141. S.514, 102d Cong., 1st Sess. (1991).

142. The preamble to this bill announces that the bill will "promote greater equity in the delivery of health care services to women through expanded research on women's issues, improved access to health care services, and the development of disease prevention activities responsive to the needs of women." *Id.*

143. National Women's Health Network at 18-19 (cited in note 48).

144. Cotton, 263 JAMA at 1050.

145. Cotton, 263 JAMA at 1049.

146. *Id.* at 1050.

many are concerned that the NIH policy will stagnate as well if it is not enforced effectively.¹⁴⁷ The apparent lack of decisive action on the part of government agencies has led doctors and women's health groups to assume that the increasing number of female researchers now entering the medical field will have to rectify the inequalities¹⁴⁸ by taking leadership roles in their own research projects.¹⁴⁹ Although the current Director of the National Institutes of Health is a woman, the need for additional women in leadership positions has yet to be fulfilled.¹⁵⁰

IV. THE LEGAL RAMIFICATIONS OF EXCLUSION

A. *Equal Protection Under the Law and the FDA Guidelines*

After expense, the most cited reason for the exclusion of women from clinical tests is the fear of teratogenic liability. Researchers and the FDA are concerned that clinical tests could harm irreparably a woman's capacity to bear children or cause harm to the fetus itself.¹⁵¹ Since a woman provides the gestation environment for a fetus, researchers fear that clinical tests could create a teratogenic environment—one that could lead to serious birth defects on the scale suffered by the Thalidomide babies in Europe.¹⁵² On the assumption that drug-related birth defects come from the mother,¹⁵³ scientists traditionally cited concern about fetal damage as a strong reason for excluding women from clinical trials.

The concern for teratogenic effects is not wholly unreasonable in light of the trauma surrounding DES.¹⁵⁴ In fact, the FDA enacted its rigorous standards specifying when fertile women can be included in clinical trials in response to the relative lack of testing of DES on

147. *Id.*

148. *Id.*

149. *Id.*

150. Eighty-five percent of the heads of NIH institutes are men. *1991 Federal Staff Directory* (Staff Directory Ltd., 1991). Fourteen of the 14 members of the House Appropriation Subcommittee on Labor, Health, Human Services, and Education are men. *1991 Congressional Staff Directory* (Staff Directory Ltd., 1991). Sixty-eight percent of pharmacists and 73% of medical researchers are men, as are 82% of all physicians. Bureau of the Census, *Statistical Abstract* at 395 (cited in note 97).

151. Council on Ethical and Judicial Affairs, 266 *JAMA* at 559 (cited in note 5).

152. Thalidomide, a drug commonly used in Europe to prevent miscarriages, caused severe birth defects, such as truncated and malformed limbs. So many children with such defects were born to mothers who had taken Thalidomide that they were collectively referred to as "Thalidomide babies."

153. Ilene Barth, *Kids at Risk From Dad's Toxic Taint*, *Newsday* 66 (April 1, 1991) (quoting Dr. Wendy Chavkin of Beth Israel Hospital and Columbia University, arguing that "[t]he bias is that it's the mother's drug use or infectious disease prior to pregnancy, not the father's, that was the problem").

154. See notes 85-93 and accompanying text.

women and its disastrous results. However, addressing the horrific results of inadequate DES testing by making it more difficult to test fertile women is problematic. This reasoning is antithetical to the FDA's purpose since the damage caused by untested drugs could be equally as harmful to fertile women, if not more so, than the damage caused by controlled clinical trials.¹⁵⁵ Since clinical trials exist to give researchers and developers of pharmaceutical products an opportunity to ascertain the negative side effects of products they market, the justification of teratogenic liability is an irreconcilable antinomy.

Additionally, since recent medical evidence indicates that many birth defects actually may be a result of sperm damage,¹⁵⁶ the constitutionality of the FDA's regulations regarding the testing of fertile women is questionable under the equal protection clause.¹⁵⁷ If the FDA is making its testing determinations on the basis of gender, then it will have to justify its policy under the intermediate standard of scrutiny that courts apply to gender based classifications.¹⁵⁸

1. *Johnson Controls*—A New Era in Equal Protection or a Holding Limited to Title VII?

A recent Supreme Court decision, *International Union v. Johnson Controls, Inc.*¹⁵⁹ discussed the interaction of Title VII of the Civil Rights Act of 1964 and the Pregnancy Discrimination Act and highlighted the nature of gender discrimination in the workplace. Although *Johnson Controls* is firmly grounded in statutory interpretation, a broader principle—one that regards discrimination on the basis of fertility as impermissible in a variety of contexts—arguably underlies the decision.¹⁶⁰

155. Cotton, 263 JAMA at 1050 (cited in note 4) (quoting Dr. Sidney Wolfe of the Public Citizens' Health Research Group, Washington D.C., arguing that "[i]t makes sense . . . to include a proper portion of groups who will use a drug in studies of that drug").

156. See notes 224-30 and accompanying text.

157. The Supreme Court of the United States has applied the equal protection clause to the federal government through the due process clause of the Fifth Amendment. See, for example, *Bolling v. Sharpe*, 347 U.S. 497 (1954); John E. Nowak and Ronald D. Rotunda, *Constitutional Law* at 569 (West, 4th ed. 1991).

158. See *Craig v. Boren*, 429 U.S. 190 (1976). Additionally, the actions of pharmaceutical manufacturers might rise to the level of state action. The state action doctrine applies to the federal government when federally protected constitutional rights are at stake. If a sufficient nexus exists between the drug companies' actions and the actions of the FDA, then drug manufacturers could be held as state actors acting in violation of the Equal Protection Clause. The nexus might exist if the FDA regulations encourage, as many commentators argue they do, drug companies to exclude women. A full discussion of the state action issue is beyond the scope of this Note.

159. 111 S. Ct. 1196 (1991).

160. When the Court decided *Johnson Controls*, the case was hailed as the "strongest and most important sex-discrimination victory in nearly 30 years." Marcia Coyle, *Fetal-Protection Ruling Buys Rights Groups*, Nat'l L. J. 5 (April 1, 1991). Additionally, many commentators

In *Johnson Controls* the United States Supreme Court held that under Title VII's bona fide occupational qualification exception¹⁶¹ and provisions relating to pregnancy discrimination,¹⁶² an employer may not discriminate against women with regard to job assignments on the basis of a woman's reproductive health.¹⁶³ By barring fertile women from jobs that could potentially harm their reproductive health, while ignoring that many of the same health hazards applied to males, the employer based its policy on gender.¹⁶⁴ The employer failed to establish that a bona fide occupational qualification which justified the exclusion of fertile women from lead-related jobs existed.¹⁶⁵ Since no bona fide reason existed for excluding women, the policy was discriminatory, and the Court held it impermissible under Title VII.¹⁶⁶

The reasoning of *Johnson Controls* can be analogized to the clinical setting. As compelling as the concern for teratogenic liability may seem in the medical context, it fails to recognize that males also can have their reproductive health damaged by clinical trials.¹⁶⁷ Damage to sperm potentially can be passed on to offspring in the form of birth defects.¹⁶⁸ Although it may be far easier to conceptualize women as the source of teratogenic effects because pregnancy is an obvious contact point for the passage of defects to offspring, evidence increasingly points to the male role in the reproductive equation as the situs of many ill effects.¹⁶⁹ There is now evidence that many toxins actually bind to sperm and cause birth defects in the children of men exposed to them.¹⁷⁰ While some toxins cycle through the male system relatively

viewed it as an expansion of substantive rights for women at a time when procedural rights in employment discrimination are shrinking. *Id.*

Some courts have begun to extrapolate from the holding in *Johnson Controls* that the possibility of tort liability is not a sufficient interest to justify what would otherwise be considered a constitutional violation. See, for example, *Flores by Galves-Maldonado v. Meese*, 942 F.2d 1352, 1364 (9th Cir. 1991) (stating that in the context of the Immigration and Naturalization Service's detention of an illegal alien's children, *Johnson Controls* stands for the proposition that avoiding lawsuits or possible tort liability does not justify a policy that violates the rights of individuals).

161. 42 U.S.C. § 2000e-2(e) (1988). This section permits some discriminatory employment practices when the practices are related to "a bona fide occupation reasonably necessary to the normal operation of that particular business or enterprise." *Id.*

162. 42 U.S.C. § 2000e(k).

163. *Johnson Controls*, 111 S. Ct. at 1203.

164. *Id.*

165. *Id.* at 1204-07. Lead has been shown to have a deleterious effect on the reproductive health of both men and women exposed to it in the course of their employment.

166. *Id.* at 1203. The Court's decision was especially appropriate in light of evidence that men often suffered the same reproductive ill effects as women.

167. See note 170 and accompanying text.

168. See notes 224-30 and accompanying text.

169. See notes 170-71 and accompanying text.

170. See Ricardo Yazigi, Randall Odem, and Kenneth Polakoski, *Demonstration of Specific Binding of Cocaine to Human Spermatozoa*, 266 JAMA 1956 (1991). See generally, Cohen, 21

quickly, other substances, such as radioactive elements, affect male reproductive health for much longer periods of time.¹⁷¹

If the Food and Drug Administration truly is concerned with preventing damage to reproductive health during clinical trials, it should be concerned that the men on whom drugs are tested could suffer some sort of deleterious effect to their reproductive systems. Such an effect might be passed on to the male subjects' offspring in the form of birth defects or might cause spontaneous abortions in their spouses. When the FDA allows pharmaceutical companies to test drugs that may damage men's reproductive health, while citing reproductive health as the reason for excluding women from the same tests, then the FDA has based its decision on gender rather than on health concerns. The grounds upon which the FDA bases its reasoning are, therefore, similar to those successfully challenged in *Johnson Controls*.

As evidenced by its continued vitality, the concern for teratogenic liability has strong appeal. Nonetheless, many of the same logical flaws that existed in the employment context in *Johnson Controls* exist in the drug testing context as well. First, as the Court recognized in *Johnson Controls*, under the Pregnancy Discrimination Act women have the right not to be discriminated against in the job arena.¹⁷² The Court also stated that women may place their future offspring at risk in performing their jobs.¹⁷³ Although the statute at issue in *Johnson Controls* specifically addressed employment discrimination on the basis of gender, the underlying rationale also extends to the area of drug testing. As in *Johnson Controls*, the rationale for excluding women on the basis of their ability to bear children does not hold up to careful scrutiny since many of the same health concerns apply to men as well.

Johnson Controls may signal that discrimination in contexts other than employment also is impermissible. Its language implies that reproductive capacity is an impermissible basis for discrimination, particularly when the same potential damage faces both males and females.¹⁷⁴ *Johnson Controls* also implies that potential damage to unborn children is not a sufficient rationale for discriminating against women.¹⁷⁵

Some might argue that the Court's earlier holding in *Geduldig v. Aiello*¹⁷⁶ forecloses this line of argument. The insurance policy at issue

Nursing Clinics of N. Am. at 49 (cited in note 24).

171. See Cohen, 21 Nursing Clinics of N. Am. at 61-62 (cited in note 24).

172. 111 S. Ct. at 1203 (citing 42 U.S.C. § 2000e(k)).

173. *Id.* at 1210.

174. *Id.* at 1203.

175. *Id.* at 1210.

176. 417 U.S. 484 (1974) (holding that discrimination on the basis of pregnancy is not gender discrimination for the purposes of the Equal Protection Clause).

in *Geduldig*, however, discriminated on the basis of pregnancy. The Court stated that a classification based on pregnancy, which by its nature only affects women, did not constitute gender discrimination because the other group included in the policy's rubric, nonpregnant persons, by definition included men and nonpregnant women.¹⁷⁷ Unlike the insurance policy in *Geduldig*, the FDA guidelines discriminate on the basis of the capacity to become pregnant, a classification that includes a far broader number of women than were covered in *Geduldig*. In fact, the exclusionary policy at issue in *Johnson Controls* considered all women under the age of 70 to be fertile unless otherwise documented.¹⁷⁸

In general, *Geduldig* has been a highly criticized case.¹⁷⁹ Over two dozen law review articles and several other analyses of constitutional doctrine agree that the case was wrongly decided.¹⁸⁰ Even the principal scholarly defense of the case agrees that the Court erred in determining that discrimination on the basis of pregnancy was not gender discrimination.¹⁸¹ The Court itself has rarely cited the decision.¹⁸² In *Turner v.*

177. *Id.* at 496-97 & n.20.

178. *Johnson Controls*, 111 S. Ct. at 1200. Interestingly, the argument that there is a distinction between classifications on the basis of pregnancy and those on the basis of capacity to become pregnant was raised in oral argument before the Court in *Bray v. Alexandria Women's Health Clinic* No. 90-985 reported in *Abortion—Ban on Obstructing Access to Clinics—42 U.S.C. 1985(3)*, 60 U.S.L.W. 3331 (Nov. 5, 1991). The federal government argued before the Court that the class at issue in *Johnson Controls* was fertile women, and that the Court should not overrule *Geduldig's* logic, because both classes at issue in *Bray*, those involved in the abortion process and those not involved, included both women and men. *Id.* at 3332. The government saw no tension between *Johnson Controls* and *Geduldig* because the former was gender discrimination based on fertility while the latter, as in *Bray*, dealt with no gender classification since the protected class included both women and men. *Id.* Counsel also argued that the discrimination in *Johnson Controls* was distinguishable because it was against women generally. *Id.* In effect, the policies of excluding fertile women from clinical trials excludes so many women that it is more like discrimination on the basis of gender than on the basis of pregnancy.

179. In her law review article, *Equality's Riddle: Pregnancy and the Equal Treatment/Special Treatment Debate*, 13 N.Y.U. Rev. L. & Soc. Change 325 (1985), Professor Wendy Williams argued that pregnancy and lactation were the only criteria that separated women from men. Professor Ann Scales similarly argued:

In observing that these are the capabilities which *really* differentiate women from men, it is crucial that we overcome any aversion to describing these functions as "unique." Uniqueness is a "trap" only in terms of an analysis, such as that generated in *Geduldig v. Aiello*, which assumes that maleness is the norm. "Unique" does not mean uniquely handicapped.

Ann Scales, *Towards a Feminist Jurisprudence*, 56 Ind. L. J. 375, 435 (1981).

180. See, for example, Nancy Erickson, *Equality Between the Sexes in the 1980's*; 28 *Cleve. St. L. Rev.* 591 (1979); Ruth Bader Ginsberg, *Gender in the Supreme Court; The 1973 and 1974 Terms*, 1975 *Sup. Ct. Rev.* 1; Laurence Tribe, *American Constitutional Law* § 16-29 (Foundation, 2d ed. 1988).

181. *Law*, 132 U. Pa. L. Rev. at 984 (cited in note 40) (citations omitted). The defenders of *Geduldig* believe that the classification could have been upheld as reasonable. See, for example, Stanley Schair, *Sex Discrimination: The Pregnancy-Related Disability Exclusion*, 49 *St. John's L. Rev.* 684 (1975).

182. The Court has cited the decision a total of 11 times as of February 1992. One case cited

*Department of Employment Security*¹⁸³ the Court limited *Geduldig's* holding to insurance claims. The Court subsequently expanded the *Geduldig* rationale to the Title VII arena in *General Electric Co. v. Gilbert*,¹⁸⁴ but Congress quickly overruled the latter decision with the passage of the pregnancy discrimination provision of Title VII.¹⁸⁵ Since that time, the Court has cited *Geduldig* only in historical recounts of the purposes of this provision.¹⁸⁶

Professor Sylvia Law has noted that *Geduldig* made it doctrinally more difficult to claim that reproductive freedom is an aspect of sex-based equality.¹⁸⁷ However, she made this argument in 1984, long before the Court's decision in *Johnson Controls*. Although *Geduldig* may still have viability to the extent that pregnancy itself may not be considered gender discrimination, the language in *Johnson Controls* indicates that the Court perceives pregnancy as unique to women, but does not see it as a condition universally descriptive of women.¹⁸⁸ The employer's policy in *Johnson Controls* excluded women because they were fertile, not because they were actually pregnant.¹⁸⁹ This language seems to extend beyond the statutory mandate of the pregnancy discrimination provision of Title VII, since under this statute even discrimination on the basis of pregnancy is impermissible unless justifiable as a bona fide occupational qualification. Therefore, the Court's distinction between fertility and pregnancy is unnecessary unless the Court is aiming towards a broader interpretation of the *Johnson Controls* holding.

In sum, the FDA has no compelling reason for preventing women from participating in clinical trials and is engaging in impermissible gender discrimination. In the employment context of *Johnson Controls*, the Court's primary concern was to safeguard a woman's right to equal employment as protected by Title VII.¹⁹⁰ In the context of clinical trials, the exclusion of women goes beyond simply the right of women to participate in those trials on a level equal to that of men. The exclusion goes to the fundamental purpose of the clinical trials themselves—to

it for the benign proposition that the Supreme Court need not decide if sex is a suspect classification. *Stanton v. Stanton*, 421 U.S. 7, 13 (1975). Other cases cited it for general equal protection arguments regarding insurance programs. See, for example, *California Savs. & Loan Ass'n v. Guerra*, 479 U.S. 272, 277 n.5 (1987).

183. 423 U.S. 44, 45 (1975).

184. 429 U.S. 125 (1976).

185. 42 U.S.C. § 2000e(k) (1988).

186. See, for example, *Guerra*, 479 U.S. at 277 n.5.

187. Law, 132 U. Pa. L. Rev. at 985 (cited in note 40).

188. *Johnson Controls*, 111 S. Ct. at 1199.

189. *Id.* at 1203.

190. *Id.* at 1210.

insure that the drugs marketed are safe for those taking them. At least one spokesman at the FDA also has come to the conclusion that *Johnson Controls* mandates that women, and not the FDA, are to make the determination of how best to protect the fetus.¹⁹¹

2. The FDA's Guidelines for Testing Fertile Women: Do They Pass Equal Protection Requirements?

In its regulation of human clinical trials, the FDA issues policy statements designed to guide both FDA administrators in approving permissible clinical trials and researchers in developing those trials.¹⁹² In its policy statement, "General Considerations for the Clinical Evaluation of Drugs" (the Guidelines), the FDA sets forth the circumstances under which clinical trials of fertile women will be permissible.¹⁹³ The FDA Guidelines provide that a woman of childbearing potential¹⁹⁴ should be excluded from the earliest dose-ranging studies.¹⁹⁵ The FDA Guidelines further state that such women also should be excluded from the second phase of clinical trials.¹⁹⁶ Large scale clinical trials may be initiated with women of childbearing potential only at the last stage of clinical testing,¹⁹⁷ and then only if sufficient information regarding the efficacy and relative safety of a drug has been accumulated and adequate reproduction studies have been completed in animals.¹⁹⁸

The FDA allows only two exceptions to this procedure. First, in studies testing drugs that have teratogenic potential but also have a life-saving or a life-prolonging quality, women who have been institutionalized for a period of time adequate to establish a nonpregnant

191. Telephone interview with Dr. Robert Temple (cited in note 43).

192. See, for example, FDA Guidelines (cited in note 39).

193. Id. at 10-11.

194. A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant, including women on oral contraceptives and women in mental institutions, but not including women in prisons. Id. at 10.

195. During this phase, investigators administer the new drug to healthy volunteers to determine the metabolic and pharmacological effects. This study usually takes one to two years to complete and uses between twenty and eighty subjects. Myron L. Marlin, *Treatment INDs: A Faster Route to Drug Approval?* 39 Am. U. L. Rev. 171, 180 (1989). These subjects are all males or postmenopausal females. Telephone interview with Dr. Robert Temple (cited in note 43).

196. FDA Guidelines at 10 (cited in note 39). Phase II studies, from which fertile women also are excluded, are controlled clinical studies to determine the efficacy of the drug and to ascertain the short term side effects and risks of the drug. These studies are closely monitored, involve several hundred subjects, and take one to two years to complete. Marlin, 39 Am. U. L. Rev. at 180 (cited in note 195).

197. The Phase III studies are expanded trials. After the evidence is accumulated from Phase I and II studies, Phase III studies allow researchers to gather additional information to evaluate the drug's overall risks and benefits. Marlin, 39 Am. U. L. Rev. at 181 (cited in note 195).

198. FDA Guidelines at 10 (cited in note 39).

state can be included.¹⁹⁹ Second, when the disease is life-threatening, but the teratogenic potential has not been established by animal studies, a fertile woman can be included in a clinical trial if she meets certain requirements. First, a fertile woman must take a pregnancy test; second, she must give her fully informed consent, after the researchers point out the lack of animal studies, and third, she must receive advice about contraceptive measures.²⁰⁰ The FDA also requires a follow-up procedure to monitor fertile women who have had drugs administered to them under either of these exceptions because a presumption exists that the drugs will be transmitted through the transplacental passage and in milk secretions.²⁰¹

By contrast, the FDA allows for the inclusion of fertile male subjects in clinical trials unless research in laboratory animals has uncovered abnormalities in the testes or in spermatogenesis.²⁰² Even if such abnormalities are detected, males still can be included in all phases of clinical trials depending on the nature of the disease, the importance of the drug, the duration of drug administration, and the dosage at which the abnormality occurred.²⁰³

The purpose of the Guidelines is to protect the fetus from teratogenic damage by limiting the participation of potential mothers in clinical trials.²⁰⁴ In light of this goal, the FDA Guidelines are both underinclusive and overinclusive. They are underinclusive because they allow women in prisons to be included in clinical trials regardless of their childbearing potential²⁰⁵ despite the fact that women in prison can become pregnant, if not while in prison, then certainly upon release. Additionally, they regularly include fertile males although testing may cause damage to the male reproductive system and cause birth defects and miscarriages as well.²⁰⁶ The FDA Guidelines are overinclusive because they include many women who do not have the potential to become pregnant. For example, the FDA Guidelines do not permit testing on women using oral contraceptives, regardless of the minimal chance of pregnancy.²⁰⁷ According to an FDA spokesman, the FDA is aware of

199. *Id.*

200. *Id.* at 10-11. In practice the latter exception has not resulted in the inclusion of women in important life-saving research. For example, the Centers for Disease Control recently advised against giving certain investigational treatments for Acquired Immune Deficiency Syndrome to pregnant women despite the life-threatening nature of the disease. Chavkin and Fox, 264 *JAMA* at 974 (cited in note 3).

201. FDA Guidelines at 11 (cited in note 39).

202. *Id.* Spermatogenesis is the creation of sperm.

203. *Id.*

204. Chavkin and Fox, 264 *JAMA* at 973 (cited in note 3).

205. FDA Guidelines at 10 (cited in note 39).

206. See notes 224-30 and accompanying text.

207. See FDA Guidelines at 10 (cited in note 39). If birth control pills are taken according to

these anomalies and currently has plans to alter its Guidelines later this year.²⁰⁸ The new Guidelines will take into account a woman's actual potential for becoming pregnant, including whether she is using contraceptives.²⁰⁹

Even if the FDA corrects these anomalies, however, the Guidelines arguably still would constitute an impermissible gender classification. First, although the Supreme Court has upheld pregnancy-based distinctions in *Geduldig v. Aiello*,²¹⁰ the Guidelines distinguish between those with the capacity to become pregnant, by definition only fertile women, and those without the capacity to become pregnant, a category that also includes postmenopausal women and, apparently, women in prison.²¹¹ Since the Guidelines do not exclude only women who are actually pregnant, they more clearly resemble the employment policy struck down in *Johnson Controls*²¹² than the disability benefits law at issue in *Geduldig*.²¹³ As the Supreme Court implicitly recognized in *Johnson Controls*, discrimination on the basis of the ability to become pregnant is a gender classification.²¹⁴

If the FDA Guidelines are based upon a gender classification, this classification must meet the requirements of the equal protection clause. Here, the standard the Supreme Court set forth in *Craig v. Boren*,²¹⁵ intermediate level scrutiny, would apply. Therefore, in order for the classification to be constitutionally permissible, the government must show an important governmental objective and the government's means must be substantially related to this objective.²¹⁶ Certainly the FDA has an important governmental interest in protecting the reproductive health of women in clinical trials and in protecting the future offspring of those women from birth defects. Whether the means the FDA has chosen are substantially related to this interest, however, is another matter.

First, by protecting only some fertile women from the dangers of clinical trials and not protecting others, the FDA fails to tailor its

their directions—one a day without missing any pills—they are about 99% effective. Robert Berkow, ed., *The Merck Manual of Diagnosis and Therapy* 1732 (Merck, Sharp and Dohme Research Laboratories, 15th ed. 1987). The actual failure rate for birth controls pills experienced by all couples taking them is 3%. *Physicians Desk Reference* 2485 (Medical Economics Data, 46th ed. 1992) (listing data on the Norplant system of birth control).

208. Telephone interview with Dr. Robert Temple (cited in note 43).

209. *Id.*

210. 417 U.S. 484 (1974).

211. See FDA Guidelines at 10 (cited in note 39).

212. 111 S. Ct. 1196 (1991).

213. 417 U.S. 484.

214. 111 S. Ct. at 1203.

215. 429 U.S. 190 (1976).

216. *Id.*

means sufficiently to its end of preventing future birth defects. For example, a female prisoner who participated in a clinical trial, became pregnant, and had a child with a birth defect would not be protected under the current FDA Guidelines, nor would a child whose father suffered harm to his reproductive capacity.

Second, since the difficulty of including fertile women in clinical trials has resulted in their exclusion from most clinical research altogether,²¹⁷ the FDA allows the release of drugs on the market with little or no understanding of their effects on women or of their potential effects on future offspring. If the goal is to protect future offspring from birth defects, then the government could require teratogenic animal studies, such as those now required before fertile women are included, and other studies to determine the teratogenic potential of the drugs.²¹⁸ Once these tests are run, the tested drugs could be marketed, as they often are now, with a statement that there is no evidence of teratogenic effects of the substance but that, since the drug has not been tested on pregnant women, it should not be used during pregnancy.²¹⁹

The exclusion of fertile women does little to effectuate the end of preventing teratogenic effects; pregnant women cannot under any circumstances be tested, so only women who are not currently pregnant would be involved. Therefore, fertile women who are informed of the potential risk and who use some form of contraception could be followed after the clinical trials to determine if there are any long term ill effects of the drug. The exclusion of such women from clinical trials does little to enhance the goal of fetal protection in the light of increasingly effective contraceptive measures. The current practice of releasing a drug with an incomplete understanding of its impact on the female physiology thus seems counterintuitive.

Third, if the goal is to protect women and future children from damage, then the exclusion of fertile women from the dose-ranging and other early phases of clinical trials does not achieve this end. According to one spokesman, the FDA believes that no scientific reason exists to mandate the inclusion of women in the early phases of clinical trials.²²⁰ Nonetheless, the spokesman concedes that there may be unknown dif-

217. See, for example, Cotton, 263 JAMA at 1050 (cited in note 4); Hamilton and Parry, J. Am. Med. Women's Ass'n at 130 (cited in note 2).

218. Gilden and Bodewitz, 32 Soc. Sci. & Med. at 1194-95 (cited in note 24).

219. See, for example, *Physicians Desk Reference* 920 (cited in note 207) (listing precautions for Prozac, and stating that although there is no evidence of teratogenic potential based on animal studies, and ethical considerations prevent the testing of pregnant women, consumption of Prozac during pregnancy is not recommended).

220. Telephone interview with Dr. Robert Temple (cited in note 43). Dr. Temple stated that although there is no compelling medical reason to include women in the early phases of clinical trials, there may be personal liberty interests involved.

ferences in proper dose levels between males and females that have not been studied.²²¹ Research following the release of many antidepressant drugs, for example, has shown that doses proper for males are not proper for, and are possibly even dangerous to females. Effective doses for women can be determined through careful dose-ranging studies performed after teratogenic trials have been run on animals. Manufacturers then would be certain that the dosages were as low as possible, yet still effective, and that the dose levels were safe for those taking them.²²²

Finally, if the government's goal is to protect future offspring, the FDA Guidelines, which carefully protect fertile women yet allow fertile men to be tested unless there is a strong risk of damage to the male reproductive system,²²³ are grossly underinclusive. Recent studies show that sperm can carry substances into the female reproductive tract and may cause birth defects in offspring.²²⁴ Malformations or behavioral abnormalities in offspring, and even spontaneous abortions,²²⁵ can result when a damaged sperm fertilizes an egg. A severely damaged sperm also can cause a type of infertility that is difficult to detect.²²⁶ Although the medical information is still preliminary and uncertain,²²⁷ it strongly suggests that many of the seventy-five percent of birth defects previ-

221. Id.

222. Investigators detect and reject nearly all drugs subsequently deemed unsafe during Phase II of the clinical trials. Marlin, 39 Am. U. L. Rev. at 180 (cited in note 195).

223. FDA Guidelines at 11 (cited in note 39).

224. Dwight E.M. Angell, *Sperm Damage Linked to Birth Defects*, Gannett News Service (available in Nexis library, Wires file) (Dec. 31, 1991). This cocaine bonding has been linked to abnormal development in the offspring of cocaine fathers. Yazigi, Odem, and Polakoski, 266 JAMA at 1956 (cited in note 170).

Exposure to chemicals in the workplace can also damage sperm. Lead has been linked to adverse effects on both male and female reproductive systems and appears to have a direct effect on the male gonads. It alters spermatogenesis and leads to increased sperm abnormalities, decreased fertility in men, and an increased abortion rate in the wives of men exposed. Cohen, 21 Nursing Clinics of N. Am. at 59 (cited in note 24). Additionally, anesthetic gases have been shown to affect the male system negatively. A large study of 49,585 operating room personnel and a control group of 23,911 health professionals showed a statistically significant increase in spontaneous abortions in the wives and congenital abnormalities in the infants of the male physicians exposed to anesthetics. An increased rate of spontaneous abortion also exists in the wives of dentists. Id.

For an interesting case study of work-related reproductive abnormalities, see Andrew F. Olshan, Kay Teschke, and Patricia A. Baird, *Birth Defects Among Offspring of Firemen*, 131 Am. J. of Epidemiology 312 (1990). See also Anne Merewood, *Father Figures—Men Bear Responsibility in Producing Healthy Babies*, Chicago Trib. 5 (Sept. 29, 1991).

225. See sources cited in note 224.

226. Anne Merewood, *Sperm Under Siege: More Than We Ever Guessed, Having a Healthy Baby May Depend on Dad*, Health 53 (April 1991).

227. Id. Medical information surrounding the contribution of toxins to male reproductive damage is sketchy because relatively few well-designed and careful studies have been conducted. See *Leading Work-Related Diseases and Injuries—United States*, 254 JAMA 1891, 1892 (1985). See also Cohen, 21 Nursing Clinics of N. Am. at 49 (cited in note 24).

ously attributed to obscure causes²²⁸ could be linked to the father. Some studies, for example, suggest that cocaine bonds to sperm. These studies further conclude that many different types of environmental and chemical factors could result in sperm damage and birth defects.²²⁹ As medical researchers uncover the paternal contribution to fetal damage, they should move away from the assumption, apparent in the current FDA regulations, that only the mother's fetal environment is important.²³⁰ If the Guidelines exist to protect fetal health by protecting the maternal environment, then they are not sufficiently related to that end. A fertile woman who is unable to participate in a clinical drug trial could become pregnant by a man who was included in the trial and still could suffer a miscarriage, or bear a child with a birth defect as a result of testing.

The FDA Guidelines could be viewed as gender neutral in the sense that the class of people allowed into clinical trials does include women, although not fertile ones.²³¹ If so, then the constitutional question becomes whether the government's ends bear a rational relationship to a permissible government goal.²³² Yet, even under the rational basis test, the FDA standard fails to pass muster. Although the goal of protecting future children from unnecessary injury is a permissible one, excluding fertile women from clinical trials is not a rational way to accomplish this end. Since the purpose of the clinical trials is to determine the negative side effects of drugs, and teratogenic environments are negative side effects, removing fertile women from the earliest stages of clinical investigation, when researchers determine most of the negative aspects

228. Ilene Barth, *Kids at Risk From Dad's Toxic Taint*, *Newsday* 66 (April 1, 1991).

229. Many chemicals, such as dibromochloropropane (a soil fumigant), carbon disulfide (used in dry cleaning), oral contraceptives during manufacture, and ethylene dibromide (a fumigant and component of leaded gasoline) have all been linked to sperm damage and adverse reproductive results. Cohen, 21 *Nursing Clinics of N. Am.* at 60-61 (cited in note 24).

Additionally, physical agents, such as heat and radiation, have been shown not only to cause adverse reproductive outcomes, but also to continue to adversely affect male reproduction and fetal development for a long time after paternal exposure. Radiation presents an especially pernicious result since it can be the cause of spontaneous mutations in offspring of exposed males many generations later. *Id.* at 62. The occurrence of certain sporadic mutations in the offspring of older fathers has been well-established. *Id.*

Men with low vitamin C levels are more apt to have genetically damaged sperm, as are men who smoke, drink alcohol or use illicit drugs. Eleven or more X-rays before conception can lead to chromosomal damage in men. Angell, *Gannett News Service* (cited in note 224).

230. See Jane Brody, *Personal Health*, *N.Y. Times* 64 (Dec. 25, 1991). See also Cohen, 21 *Nursing Clinics of N. Am.* at 62 (cited in note 24) (arguing that "[t]he question of whether or not teratogens can act through the male is complex. . . . Yet, we must remember that it was not long ago that the placenta was assumed to be an impenetrable barrier between mother and fetus. This field is ripe for further well-designed and careful investigation.")

231. See *Geduldig v. Aiello*, 417 U.S. 484 (1974).

232. *Id.*

of drugs,²³³ means that many drugs are released for use by fertile women without an understanding of the potential effects on those women. The exclusion of fertile women does little to increase the safety of their future children and, in fact, may lead to another DES-type crisis.²³⁴ The best way to protect future offspring, then, is to determine early in the clinical testing process whether there will be a teratogenic effect either from the mother or the father, a result that is not achieved when women are excluded from drug trials altogether.

B. *Liability of Drug Manufacturers*

The pharmaceutical houses apparently have made a kind of cost-benefit analysis—weighing the cost of including fertile women in clinical trials or possibly having to run trials twice, once on men and once on women, versus the liability for releasing a relatively untested drug—and have decided that the former would be more costly than the latter. However, the pharmaceutical companies bankrupted as a result of the DES crisis, a classic example of teratogenic liability on a grand scale,²³⁵ probably would disagree with this conclusion.

1. *Liability for Damage During Clinical Trials*

Although human participants in clinical trials sign detailed and thorough informed consent forms,²³⁶ pharmaceutical companies and researchers still fear that should a fertile woman participate in a test and suffer some damage to her reproductive health, a consent form would not protect them from liability.²³⁷ Informed consent forms have been struck down by courts as invalid in other contexts.²³⁸ To date, however, apparently no suit has been brought against a pharmaceutical house for damage caused during a clinical trial.

The federal government requires that researchers obtain the informed consent of participants before they proceed with clinical trials. The specific content of the informed consent also is regulated by the government.²³⁹ All research supported by federal funds must comply with these informed consent standards, which include a description of

233. See Marlin, 39 Am. U. L. Rev. at 180 (cited in note 195). Additional studies have linked the use of tobacco and alcohol by fathers to sperm damage, birth defects and a whole host of childhood diseases.

234. Saunders and Saunders, 11 Health Care for Women Int'l at 424-25 (cited in note 24).

235. See *id.* at 423-25, 429-30.

236. See FDA Guidelines at 2 (cited in note 39).

237. Chavkin and Fox, 264 JAMA at 973 (cited in note 3).

238. For example, a doctor cannot force his patient to sign a consent form absolving the doctor of liability for negligence.

239. 45 C.F.R. § 46.116 (1991) (setting forth general requirements for informed consent).

any reasonably foreseeable risks or discomforts, a description of any benefits the subject will receive, and a statement that participation is completely voluntary and can be discontinued at any time.²⁴⁰ The regulations further provide that if the research involves more than minimal risk, an explanation as to whether any compensation or treatments for injury will be available must be given to the subject.²⁴¹ Despite these regulations, researchers fear that a court faced with a child suffering from a birth defect would find these standard consent forms invalid with little hesitation.²⁴²

Some members of the medical profession take exception to this assumption.²⁴³ They argue that the concern for liability, despite the existence of consent forms, is based on the assumption that an adult woman is not competent to make an informed decision regarding her participation in a clinical trial, in spite of a process by which she is made to understand the risks and benefits to her own health and possible risks to an embryo.²⁴⁴ These medical professionals also refute the assumption that, if a woman in a clinical trial suffers a contraceptive failure, she could not make a responsible and intelligent determination whether or not to terminate the pregnancy or carry the fetus to term.²⁴⁵ Presumably, private pharmaceutical companies fear tort liability if she continues the pregnancy and gives birth to a damaged child. This concern, however, should be minimized if honest and thorough informed consent procedures are followed.²⁴⁶ The government may fear that the woman will decide to abort the fetus. Commentators believe that the government prefers to avoid all situations in which the abortion controversy may arise.²⁴⁷ In sum, the decision to exclude fertile women from clinical trials is an example of legal and political considerations "unduly influencing" health and research policy decisions.²⁴⁸

Another, more valid, concern on the part of drug manufacturers is not that the woman herself would bring suit, but that her child would bring suit as a result of birth defects. The general rule is that parents cannot waive causes of action on behalf of their children,²⁴⁹ and virtu-

240. *Id.* §§ 46.116(a)(2)-(3), (8).

241. *Id.* § 46.116(a)(6).

242. Dr. Temple of the FDA stated that anyone who knew anything about the courts in this country would know the consent forms were not worth anything should a birth defect actually occur. Telephone interview with Dr. Robert Temple (cited in note 43).

243. See, for example, Chavkin and Fox, 264 *JAMA* at 973-74 (cited in note 3).

244. *Id.* at 973.

245. *Id.*

246. *Id.*

247. *Id.* at 973-74.

248. Thomas C. Chalmers, M.D., *In Reply*, 264 *JAMA* 974 (1990) (responding to Chavkin and Fox, 264 *JAMA* at 973 (cited in note 3)).

249. See, for example, *Johnson Controls*, 111 S. Ct. at 1211 & 1211 n.3 (White concurring).

ally all jurisdictions allow tort claims for prenatal injuries provided the child is born alive.²⁵⁰ Nevertheless, because there are various reliable ways of protecting against pregnancy during the course of the trial, the concern that there would be liability as a result of damage done to a fetus during clinical trials is not well-founded. A woman could agree, as part of her consent to clinical trials, that she would abstain from sexual intercourse for the duration of the trial or that she would use the most reliable form of birth control available to prevent pregnancy.

Norplant,²⁵¹ for example, is a form of birth control that is extremely effective—even more effective than female sterilization.²⁵² Norplant is used easily, and when the implant is removed, fertility returns quickly.²⁵³ A woman could agree to have Norplant installed for the period of the clinical trials and removed once the trials were completed. Additionally, women who have been sterilized by tubal ligation²⁵⁴ have the same hormonal cycles and menstruate like women who are completely fertile.²⁵⁵ Since one of the major problems with the failure to test drugs on fertile women is the uncertainty regarding effects during women's cycles, utilizing women who have been surgically sterilized, yet who retain the hormonal structure of fertile women, would address both the dangers of excluding fertile women and the fear of teratogenic liability.

If the FDA were to require pharmaceutical houses to include fertile women, or at least women with the cycles of fertile women in their clinical trials, the drug companies could limit their legal exposure. If the informed consent signed by a woman before a clinical trial contained an agreement to use Norplant, and a failure of the system resulted in injury to a child, it would be difficult for the child to argue that the pharmaceutical companies failed to take due care to prevent the injury. In fact, the companies would have taken the best precautions available, so the chance of their being found negligent would be

250. *Id.* at 1210-11 (citing W. Page Keeton et al., *Prosser & Keeton on the Law of Torts* § 55 at 368 (West, 5th ed. 1984)).

251. The Norplant System is a group of six levonorgestrel (a progestin) implants which are installed under a woman's skin using a local anesthetic. It can be installed in a ten to fifteen minute office visit. It prevents contraception with a continuous dose of hormones that are released into the body. *Physicians Desk Reference* at 2484-88 (cited in note 207).

252. Norplant has an expected failure rate of 0.2% during the first year of use. Its typical failure rate (the actual failure rate experienced by users of the system) is also 0.2%. It is currently the most effective form of birth control next to male sterilization, which has an expected failure rate of 0.1% and a typical failure rate of 0.15%. By contrast, female sterilization has an expected failure rate of 0.2%, but a typical failure rate of 0.4%. *Id.* at 2485 table 2.

253. *Id.* at 2485.

254. Tubal ligation is the tying of the fallopian tubes.

255. R. Rivera, et al., *Menstrual Patterns and Progesterone Circulating Levels Following Different Procedures of Tubal Occlusion*, *Contraception* 157 (Aug. 1989).

very slight.

If a pharmaceutical house were to require, as part of its informed consent agreement, that those participating in its clinical trials abstain from sexual intercourse for the duration of the study, and a woman failed to adhere to the agreement and became pregnant, her willful conduct would break the chain of causation between the pharmaceutical company and the child's injuries. At one time, a court might have wanted to circumvent this causation principle in order to allow the child some sort of recovery. The trend now, however, is increasingly toward the elimination of parent-child immunity—meaning that an injured child could sue his mother for his or her injuries.²⁵⁶ Furthermore, genetic testing often can determine whether a fetus contains a potential birth defect in time for an abortion should an anomaly be detected.²⁵⁷ At least one court has suggested that a child born with severe birth defects could successfully sue the mother for her failure to obtain an abortion in light of her knowledge that the child would be born defective.²⁵⁸

Even if there is potential liability for damage caused in clinical testing despite rigorous informed consent, such concerns pale when compared to the risk posed by a drug that is released on the market without sufficient testing. The nightmare that followed the administration of DES to pregnant women provides the best example of this problem.²⁵⁹ The FDA hopes to prevent another DES situation by requiring all of the teratogenous studies to be completed on animals before fertile women are included in clinical trials.²⁶⁰ As with many drugs not exclusively for use by women, this requirement effectively operates to bar fertile women from clinical trials.²⁶¹ Thus, the potential teratogenic ef-

256. For a discussion of the issues surrounding such suits, see Ron Beal, "Can I Sue Mommy?": An Analysis of a Woman's Tort Liability for Prenatal Injuries to Her Child Born Alive, 21 San Diego L. Rev. 325 (1984).

257. For a discussion of the limits on genetic screening and potential abuses in the employment context, see Larry Gostin, *Genetic Discrimination: The Use of Genetically Based Diagnostic and Prognostic Tests by Employers and Insurers*, 17 Am. J. L. & Med. 109 (1991).

258. *Curlender v. Bio-Science Laboratories*, 106 Cal. App. 3d 811, 165 Cal. Rptr. 477, 488 (1980) (observing that there is "no sound public policy which should protect those parents from being answerable for the pain, suffering and misery which they have wrought upon their offspring").

The California legislature acted quickly in response to this suggestion by passing in 1981 § 43.6 of the Civil Code, which relieves parents of any liability for not having an abortion and provides that it is no defense in any action against a third party that an abortion could have been obtained. Cal. Civil Code § 43.6(a)-(b) (West 1982). Additionally, the choice not to have an abortion cannot be figured into a damage award. *Turpin v. Sortini*, 31 Cal. 3d 220, 643 P.2d 954, 182 Cal. Rptr. 337 (1982).

259. Saunders and Saunders, 11 Health Care for Women Int'l at 424-25 (cited in note 24).

260. FDA Guidelines at 10 (cited in note 39).

261. See Chavkin and Fox, 264 JAMA at 973 (cited in note 3).

fects of many commonly used drugs remains unknown.

The point of clinical trials is to determine if there will be any ill effects from the drug. Without clinical trials, many side effects remain undetected until after the drug has been released to the general populace, as was the case with DES.²⁶² The clinical trials exist to assess the potentially damaging effects of a drug and either to rectify them when possible or at least to warn users of the potential risks. With drugs tested exclusively on males, pharmaceutical houses risk much greater liability by releasing a drug on the market with an incomplete understanding of the potential risk to women.²⁶³ Thus, the exclusion of fertile women from clinical trials may actually expose pharmaceutical companies to significant liability despite the ostensibly noble goal of protecting women.²⁶⁴

2. Liability for Damage Caused by Relatively Untested Drugs

A drug manufacturer has a duty to distribute a product that is fit for its intended purpose.²⁶⁵ The mere fact that the FDA has approved a drug for marketing does not insulate pharmaceutical manufacturers from liability for damage caused by that drug.²⁶⁶ The Supreme Court has been reluctant to find that FDA regulations preempt state tort law,²⁶⁷ and a majority of states have held that compliance with FDA standards is insufficient to immunize the drug manufacturer from state tort claims.²⁶⁸ One of the requirements for a finding of implied preemption of state court claims is that the federal and state law interests be in conflict.²⁶⁹ Since the goal of both the FDA regulations and state tort law

262. Saunders and Saunders, 11 *Health Care for Women Int'l* at 424-25 (cited at note 24).

263. See notes 49-95 and accompanying text.

264. *Id.*

265. See *Feldman v. Lederle*, 97 N.J. 429, 479 A.2d 374 (1984).

266. See, for example, *Abbot v. American Cyanamid*, 844 F.2d 1108 (4th Cir. 1988); *Hurley v. Lederle*, 851 F.2d 1536 (5th Cir. 1988). But see *Grundberg v. Upjohn*, 813 P.2d 89 (Utah 1991) (holding that FDA approved prescription drugs are unavoidably dangerous in design; therefore, manufacturers are immune from strict liability).

267. See *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (stating that state police powers are not superseded by federal law "unless that [is] the clear and manifest purpose of Congress").

268. See, for example, *Graham v. Wyeth Laboratories*, 666 F. Supp. 1483, 1493 (D. Kan. 1987) (stating that "[w]hile Congress intends vaccines to be at least as uniformly safe as the FDA regulations require, there has never been a congressional intent that innocent victims of adverse reactions should be precluded from being compensated"); *MacDonald v. Ortho Pharmaceutical Corp.*, 394 Mass. 131, 475 N.E. 2d 65 (1985) (stating that compliance with the FDA standards was not a shield against state tort liability); *Feldman*, 479 A.2d at 383 (stating that regulation by the FDA will not insulate drug manufacturers from liability).

269. Comment, *Federal Preemption and the FDA: What Does Congress Want?* 58 U. Cin. L. Rev. 263, 266 (1989) (citing *Hillborough County, Fla. v. Automated Medical Laboratories*, 471 U.S. 707, 713 (1985)). Since the FDA regulations do not expressly preempt state tort law, the

is to provide the consumer with safe and effective pharmaceutical products,²⁷⁰ courts view state tort actions as increasing the incentive for drug manufacturers to improve the quality and safety of their products.²⁷¹ Allowing pharmaceutical manufacturers to use FDA compliance as immunization from liability would defeat the purposes behind both the FDA regulations and state tort law. Courts, therefore, are understandably reluctant to find preemption in the pharmaceutical context.²⁷²

Whether pharmaceutical manufacturers should be held to a negligence or a strict liability standard has been the subject of much discussion.²⁷³ Most states have adopted the Restatement Second of Torts Section 402A's requirement of strict liability for pharmaceutical products.²⁷⁴ Those states which have adopted this rule often mitigate it by the use of Comment k to the Restatement,²⁷⁵ which insulates manufacturers of unavoidably unsafe products from strict liability. These states, however, do not find that Comment k insulates all drug manufacturers

courts use a three-part standard to determine if there is implied preemption: first, the comprehensive nature of the federal regulations; second, the dominant federal interest in the matter regulated; and third, whether there is a direct conflict between state tort law and the federal regulations. The Supreme Court has been reluctant to find implied preemption of state claims with a comprehensive federal statute, and is even more reluctant to do so with regard to comprehensive federal regulation. *Id.*

270. *MacGillivray v. Lederle Laboratories*, 667 F. Supp. 743, 745 (D.N.M. 1987) (reasoning that the object of the FDA regulations is to provide safe and effective drugs to the public and rejecting a drug manufacturer's claim of preemption).

271. See *Graham*, 666 F. Supp. at 1493.

272. For a good general discussion of preemption of state court claims for defects in drugs, see Comment, 58 U. Cin. L. Rev. at 263 (cited in note 269). See also Federick H. Fern and Lewis Bartell, *Federal Preemption of Pharmaceutical Labeling*, For the Defense 20 (July 1987), for a discussion of the history of the preemption doctrine with regard to pharmaceutical products and an argument for more court deference to the FDA at least in the context of pharmaceutical labeling.

273. See Richard C. Ausness, *Unavoidably Unsafe Products and Strict Products Liability: What Liability Rule Should be Applied to the Sellers of Pharmaceutical Products?*, 78 Ky. L. J. 705 (1989-90); Comment, *Comment k Immunity to Strict Liability: Should All Prescription Drugs Be Protected?* 26 Houston L. Rev. 707 (1989); Note, *A Prescription for Applying Strict Liability: Not All Drugs Deserve Comment k Immunization*, 21 Ariz. St. L. J. 809 (1989). Section 402A establishes strict liability for some manufacturers of unsafe products. Comment k creates an exception to this rule. Comment k provides, in part, that:

[t]here are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. . . . The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability.

Restatement (Second) of Torts § 402A Comment k (1965).

274. See, for example, *Feldman*, 479 A.2d at 381-82; *Savina v. Sterling Drug*, 247 Kan. 105, 795 P.2d 915 (1990). Most states have followed the rule enunciated in *Feldman*. Ausness, 78 Ky. L. J. at 733 (cited in note 273).

275. See, for example, *Feldman*, 479 A.2d at 381-382; *Grundberg*, 813 P.2d 89, 92-95.

on the basis that all their products are unavoidably unsafe.²⁷⁶ Those states that use a strict liability standard for breach of warranty, but recognize compliance with federal regulations as evidence that the product is unavoidably unsafe, fall back on a negligence standard for pharmaceutical products.²⁷⁷

Under the strict liability standard, when the defect consists of an improper design or warning, the reasonableness of the manufacturer in marketing the product is a factor in determining liability.²⁷⁸ The issue in these cases is whether the manufacturer knew of the defect in the product and acted in a reasonably prudent manner in marketing the product or in providing a warning.²⁷⁹ Once it is shown that the manufacturer knew or should have known that the drug would cause injury, the focus is on the reasonableness of the manufacturer's conduct, much like a negligence standard.²⁸⁰ The manufacturer bears the burden of proving that its actions were reasonable in light of the expert knowledge in the field.²⁸¹ The manufacturer also bears the burden of proving that it was unable to discover the defect.²⁸² Finally, a manufacturer can insulate itself from liability by giving an adequate warning.²⁸³

Under a strict liability standard, a pharmaceutical manufacturer could be held liable for any damage caused to females by drugs tested solely on a male physiology. Females damaged by relatively untested drugs can show that the manufacturer either knew or should have known that the drug would cause injury and failed to warn of that dan-

276. See, for example, *Feldman*, 479 A.2d at 383. Compare cases which state that Comment k does not apply to all pharmaceutical products, such as *Hill v. Searle Laboratories*, 884 F.2d 1064, 1068-69 (8th Cir. 1989); *Toner v. Lederle Laboratories*, 779 F.2d 1429, 1433 (9th Cir. 1986), with cases which hold that Comment k applies to all prescription drugs, such as *McElhaney v. Eli Lilly & Co.*, 575 F. Supp. 228, 230-31 (D.S.D. 1983).

Courts are more willing to apply the more lenient Comment k standard than the more rigorous risk-utility standard of strict liability when the risks are scientifically unknowable. Some courts apply the Comment k standard when the risk is unavoidable in the sense that it would entail changing the inherent nature of the product. The latter application of Comment k is the subject of dispute in many jurisdictions, and some courts hold Comment k inapplicable if the manufacturer did not take reasonable steps to limit the danger of the product even if that product is useful and desirable. *Ausness*, 78 Ky. L. J. at 726-27 (cited in note 273) (citations omitted). It would be difficult for a pharmaceutical company to argue that a risk to women was unknowable when it could easily include either sterilized women or women on Norplant in its study population and methodically study the different reactions to the product of the men and women in the study.

277. See, for example, *Baldino v. Castagna*, 308 Pa. Super. 506, 454 A.2d 1012, 1020 (1982); *Grundberg*, 813 P.2d at 92-93.

278. See, for example, *Feldman*, 479 A.2d at 385-86. See generally Fern and Bartell, For the Defense at 20 (July 1987) (cited in note 272).

279. *Id.*; See also *Barson v. Squibb*, 682 P.2d 832, 835 (Utah 1984).

280. *Feldman*, 479 A.2d at 385-86.

281. *Id.* at 386-87.

282. *Id.*

283. See also *Barson*, 682 P.2d at 835.

ger. Although pharmaceutical researchers have relied on the assumption that the male and female physiologies are analogous, the medical community, women's organizations, and even the NIH have known for years that this is not the case.²⁸⁴ If a drug was not tested for safety and effectiveness on the population targeted for its use, and this failure to test results in injury to that population, then it is inadvisable to market that drug on a wide scale. The courts assume that pharmaceutical houses have all the information of experts in the field.²⁸⁵ Because experts in the medical field understand the dangers of marketing drugs for women that are not tested on women, pharmaceutical manufacturers would not meet the second requirement of the strict liability test. Their actions in marketing these drugs simply are not reasonable. Furthermore, since it is possible, although expensive and fraught with administrative hurdles,²⁸⁶ to run clinical tests on fertile women to determine the extent to which the products are unsafe, pharmaceutical manufacturers cannot claim that any drug marketed for women, but not tested on them, is unavoidably unsafe.

Alternatively, under a negligence standard, the person injured bears the burden of showing that the manufacturer breached a duty which resulted in the alleged injury.²⁸⁷ Nevertheless, pharmaceutical manufacturers are considered experts in their field, and constructive knowledge of developments concerning their products, measured by scientific literature and other means, is imputed to them.²⁸⁸ Under the negligence standard, manufacturers have a duty to make a timely and adequate warning either to the ultimate consumer or to a learned intermediary.²⁸⁹ If the manufacturer knew or should have known about a danger, it still can be subject to liability even if all the government requirements are met.²⁹⁰

From a negligence perspective, a pharmaceutical house that has created and marketed a new drug for use by both genders cannot rea-

284. See notes 95-150 and accompanying text.

285. See note 281.

286. FDA Guidelines at 10-11 (cited in note 39).

287. See, for example, *Baldino*, 454 A.2d at 1012.

288. See, for example, *Barson*, 682 P.2d at 835.

289. See, for example, *MacDonald v. Ortho Pharmaceutical Corp.*, 394 Mass. 131, 475 N.E.2d 65, 69 (1985). See generally Frederick H. Fern, *The Decline and Fall of the Learned Intermediary Doctrine*, For the Defense 10 (Sept. 1986); Note, *The Decline of the Learned Intermediary Doctrine in Favor of Direct Patient Warnings of Drug Product Risks*, 43 Ark. L. Rev. 821 (1990).

Actually physicians use more prescription drugs than other medical procedures. This results in more side effects and related injuries, however. Physicians disclose little, if any, information regarding the risks of these treatments. Gerald F. Tietz, *Informed Consent in the Prescription Drug Context: The Special Case*, 61 Wash. L. Rev. 367, 367 (1986).

290. See *Grundberg*, 813 P.2d at 97-98.

sonably argue that it is completely unaware of current medical knowledge that drugs tested only on men are not always safe for use by women. In fact, this knowledge is imputed to them.²⁹¹ The refusal to acknowledge that the past practices in testing and marketing drugs have resulted in inferior health care for women is no defense to a negligence claim since pharmaceutical manufacturers are under a duty to keep abreast of current developments.²⁹² In light of the federal government's acknowledgement, through the NIH, that past practices in testing and marketing drugs have resulted in inferior health care for women, a manufacturer cannot reasonably argue that it was unaware of the potential dangers to women of the drugs it markets.

Thus, under either a strict liability or a negligence standard, a manufacturer could be liable for damage caused to females by drugs that were tested solely on males or designed for a male physiology. The manufacturer's compliance with FDA regulations would not be a defense.²⁹³

3. Failure to Warn

A pharmaceutical house might limit or eliminate its liability by issuing a proper warning that a drug may not be safe for use by fertile women. Under a negligence or strict liability standard, the manufacturer's failure to warn of a danger in a drug that the manufacturer knew or should have known about subjects the manufacturer to liability.²⁹⁴ Many states hold that the failure to warn of a known danger is negligence per se, whether that knowledge was constructive or actual.²⁹⁵

The difficulty of a warning in the present context comes in two forms. First, a warning's efficacy is a serious concern. To be liable for a failure to warn, the individual injured must show that she would not have used the drug had a proper warning been given.²⁹⁶ In the context of pharmaceutical products, this argument is problematic since pharmaceutical products are often necessary for the treatment of illnesses and most products used to treat serious illnesses have been tested only on

291. See *Barson*, 682 P.2d at 835-36.

292. *Id.*

293. See, for example, *Malek v. Lederle*, 466 N.E.2d 1038 (Ill. App. 1984).

294. See *id.* See also *Hasler v. United States*, 517 F. Supp. 1262 (E.D. Mich. 1981).

295. See, for example, *Barson*, 682 P.2d at 835. A drug manufacturer must warn about the dangers of its product even if the utility of the drug outweighs the risk. It will be held strictly liable for the failure to do so. *Ausness*, 78 Ky. L. J. at 716 (cited in note 273).

Pharmaceutical manufacturers are required to warn even if the risk affects only a small proportion of the products' users. *Id.* at 717. Women are the primary users of pharmaceutical products so they should be entitled to a warning that the drugs they are using might not be safe.

296. See, for example, *MacDonald*, 475 N.E.2d at 72.

men.²⁹⁷ The presence or absence of such a warning might not make any difference to a woman's choice.

Second, when the manufacturer warns that a drug is not safe for use by over one-half of the population,²⁹⁸ a pharmaceutical company's financial interests are seriously implicated. Such a warning would not be in a company's best interests regardless of the limitation it might place on its liability. Not only would this type of warning have serious and frightening consequences for women's health care, it would be economically disadvantageous for pharmaceutical houses.²⁹⁹ On the other hand, this seemingly impossible conundrum for pharmaceutical houses—warn and suffer the economic consequences or fail to warn and be subject to liability—could be the very impetus needed to encourage manufacturers to begin to include women in their clinical trials.

V. SOLUTIONS

A. *Administrative Solutions*

1. Lighting a Fire Under the NIH

One possible course of action for those who criticize the NIH's failure to enforce its own policy regarding the inclusion of women in clinical trials is to push the agency toward enforcement. Although enforcement decisions generally are committed to agency discretion by law and not judicially reviewable,³⁰⁰ judicial review is warranted when an agency has completely abdicated its enforcement responsibility.³⁰¹ When an agency's failure to observe its own regulations or procedures results in prejudice to the parties the regulations and procedures were designed to protect, the courts will force the federal agency to comply strictly with the guidelines set.³⁰²

The Supreme Court has been concerned that allowing judicial review of agency determinations would substitute the courts' assessment of which enforcement actions should take precedence for that of the

297. See Cotton, 263 JAMA at 1049-50 (cited in note 4).

298. See note 97.

299. This is especially true since women are their best customers. Hamilton and Parry, J. Am. Med. Women's Ass'n at 126 (cited in note 2).

300. See *Heckler v. Chaney*, 470 U.S. 821, 837 (1985).

301. *Adams v. Richardson*, 480 F.2d 1159, 1163 (D.C. Cir. 1973). In *Adams v. Richardson*, the court held that the Secretary of Health, Education and Welfare's decision to encourage voluntary compliance with desegregation orders was an abdication of its statutory duty. *Id.* at 1164.

The Supreme Court cited this decision in *Heckler*, 470 U.S. at 833 n.4. Although the Court stated that judicial review of enforcement decisions generally was not permissible, it expressed no opinion as to whether, when the agency decisions regarding enforcement amounted to an abdication of the agency's duty, review might be appropriate. *Id.*

302. *Baltimore v. Mathews*, 562 F.2d 914, 922 n.6 (4th Cir. 1977) rev'd on other grounds, 571 F.2d 1273 (4th Cir. 1978).

agency.³⁰³ In the context of normal enforcement decisions, this concern is valid. However, in the context of an agency's failure to act pursuant to its statutory duty, or even when the agency merely ignores its opportunities to act,³⁰⁴ the agency is not making policy determinations. Rather, it simply is deciding not to act at all, under any circumstances. In such a situation, the intervention of the courts is appropriate.³⁰⁵

The NIH already has made its policy decision. Before the NIH will fund an applicant, the applicant must show that the proposed study includes women or that a very good reason exists why women are not included.³⁰⁶ This requirement is a condition precedent to the receipt of an NIH grant.³⁰⁷ Any decision on the part of the NIH not to enforce its policy is, therefore, a failure of this agency to adhere to its own criteria.

Once an agency sets its procedural requirements, those requirements operate as if they were statutory mandates for the agency.³⁰⁸ The NIH's failure to adhere to its own policy is an abdication of its statutory duty—an abdication that injures the very people the policy was designed to protect. Furthermore, even if the NIH were to assume that researchers voluntarily would include women in their studies, as the FDA has assumed vis-a-vis pharmaceutical houses,³⁰⁹ this assumption still would not satisfy the legal requirements surrounding enforcement decisions. It is simply not enough to hope that a policy will be self-actualizing.³¹⁰ The agency must act, at least to some degree, to implement and to bring about adherence to the agency policy.³¹¹ One way to assure the inclusion of women would be to enlist the aid of the courts in forcing the NIH to follow its own policy decisions.

2. FDA Guidelines—Encouraging a More Balanced Solution

According to one spokesman at the FDA, the agency has become aware, in the light of *Johnson Controls*, that a liberty interest may exist

303. See *Heckler*, 470 U.S. at 830-32.

304. See *Adams*, 480 F.2d at 1164.

305. See *id.*

306. See text accompanying note 128.

307. *Id.*

308. *Mathews*, 562 F.2d at 920.

309. Cotton, 263 JAMA at 1050 (cited in note 4) (quoting a representative from the Pharmaceutical Manufacturer's Association); Telephone interview with Dr. Robert Temple (cited in note 43) (stating that the pharmaceutical companies are concerned about the bottom line and do not want to alienate a large portion of their consumer base).

310. See *Adams*, 480 F.2d at 1164 (noting that the Department of Health, Education, and Welfare made no formal complaints, did not file any enforcement proceedings, and did not refer cases to the Justice Department, and concluding that HEW "may not neglect this area of its responsibility").

311. *Id.*

in allowing fertile women to participate in clinical trials.³¹² Furthermore, he states that the FDA is willing to modify its Guidelines in order to comport with current scientific knowledge and with women's interests in adequate health care.³¹³ Moreover, he predicts that the GAO will find that women, even fertile ones, have been included in clinical trials all along.³¹⁴ What is clear, however, is that fertile women have not been included in the early phases of clinical research, a practice that the FDA acknowledges may be due to a lack of understanding of the differences between the male and female physiology.³¹⁵

The FDA should be encouraged to modify its Guidelines to provide a more tailored approach for pharmaceutical companies and researchers to follow. If products, such as antidepressants, are to be used predominantly by females, and the effects of those drugs will vary with the menstrual cycle,³¹⁶ then the FDA Guidelines should be flexible enough to allow fertile women to be included in all phases of the study. The clinical study populations should accurately reflect the populations that will be using the drugs.³¹⁷ Currently, there is little knowledge about how the menstrual cycle affects the pharmacokinetics of many products regularly used by women.³¹⁸ A guideline which requires gender differences to be delineated and which provides for the inclusion of fertile women in all phases of clinical trials would better account for the differences between the genders, differences that are more significant than originally thought.³¹⁹ It is precisely because of these differences that the medical community believes women, especially fertile women, should be included in all stages of clinical research.³²⁰ The changes to the guidelines currently proposed by the FDA³²¹ will be an improvement over the existing guidelines. Nevertheless, they are insufficient to address the breadth of the problem facing women and their doctors.

*B. Economic/Market Solution—Encouraging the Drug
Manufacturers*

The FDA realizes that pharmaceutical manufacturers are concerned with their own economic well being.³²² Thus, the FDA believes

312. Telephone interview with Dr. Robert Temple (cited in note 43).

313. *Id.*

314. *Id.*

315. *Id.*

316. See, for example, Raskin, 159 *J. Nerv. & Ment. Dis.* at 120 (cited in note 1).

317. Cotton, 263 *JAMA* at 1050 (cited in note 4) (quoting Dr. Sidney Wolfe).

318. See note 28 and accompanying text; part II.B.

319. See Council on Ethical and Judicial Affairs, 266 *JAMA* at 559 (cited in note 5).

320. *Id.*

321. See notes 207-08 and accompanying text.

322. See Cotton, 263 *JAMA* at 1049. This is only natural since pharmaceutical companies are

that the pharmaceutical manufacturers will include populations that reflect the actual consumers of their products.³²³ This belief, however, has not been borne out by practice.³²⁴

Yet, if pharmaceutical houses were convinced that by failing to study women's reactions to their products, they would suffer exposure to tort liability and added expense, then they would likely work to insure that women are included in their sample populations. Nevertheless, merely including women is not a satisfactory result unless differences between men and women also are studied. Competition in the international market could go a long way to encourage this result. Currently, the Japanese pharmaceutical houses are working to delineate differences between the genders and among the races.³²⁵ American and Swiss manufacturers, however, are conducting business as usual.³²⁶ Although the American and Swiss manufacturers currently control the majority of the pharmaceutical market in this country, that statistic could change. As one commentator has observed, pharmaceutical houses could make a fortune tailoring their products to women's cycles.³²⁷

VI. CONCLUSION

Regardless of the ostensibly noble reasons for the exclusion of women from clinical trials, the net result has been inferior health care for women. Women's health care has suffered from the lack of knowledge about women's physiology and from the production of drugs which are ill-suited for women's cycles.

Bernadine Healy, the new director of the NIH, has argued forcefully for the inclusion of women in clinical research, stating that medical researchers should undertake broad exploration and dismiss useless forms of discrimination. It is naive, she argues, to hope that the numbers of women currently entering the research fields will begin to correct these discrepancies on their own. Rather, it is necessary to train those in the medical profession to look for the differences between the genders.³²⁸

To this end, the FDA and the NIH, along with pharmaceutical

in business to make money.

323. Cotton, 263 JAMA at 1049.

324. *Id.*; Council on Ethical and Judicial Affairs, 266 JAMA at 559.

325. Cotton, 263 JAMA at 1050 (cited in note 4).

326. *Id.* (quoting Werner Kalow, MD, professor emeritus in the University of Toronto pharmacology department: "American and Swiss manufacturers couldn't care less").

327. Cotton, 263 JAMA at 1055 (cited in note 20) (quoting Michelle Harrison, M.D., assistant professor of psychiatry, University of Pittsburgh).

328. Healy, 266 JAMA at 566 (cited in note 129).

manufacturers, should be encouraged to create test populations in their clinical trials that reflect the populations affected. If the pharmaceutical houses and researchers actively begin to delineate gender differences, the net gain will be significant, not just for women's health care, but for the health of the nation.

The legal community is in a position to encourage this action through litigation, forcing the NIH actively to implement its policy mandating the inclusion of women and to conduct mandatory studies to differentiate gender responses. Additionally, the legal community can address the equal protection questions surrounding the FDA's Guidelines. If the FDA could be convinced that it needs to alter its Guidelines to comport with equal protection principles, steps could be taken to insure that women are included in study populations to the extent that they are consumers of the drugs. As a result, pharmaceutical manufacturers would be forced to include women in their test populations before releasing a drug onto the market. Finally, the legal community is in a strong position to make clear to pharmaceutical houses that they face potential tort liability for the inferior process by which their drugs are tested, regardless of any action by the FDA.

Ultimately, however, Congress is in the best position to mandate a health care initiative for women. Congress should be encouraged to pass the Women's Health Equity Act, which would improve the methodology of health care research. The Act would provide both the mandate and the funding for the NIH study of women's diseases. This statement of congressional intent would go a long way toward effecting the goal of providing equitable health care for women and would provide a forum through which the complex issues surrounding the safe use of women in clinical trials could be more effectively addressed.

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