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Jack & Jill Take Lots of Pills, but Jill Comes Tumbling After: Gender Inequality in Privately Funded Early Phase Clinical Trials

Shana F. Oppenheim

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JACK & JILL TAKE LOTS OF PILLS, BUT JILL COMES
TUMBLING AFTER: GENDER INEQUALITY IN PRIVATELY
FUNDED EARLY PHASE CLINICAL TRIALS

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INTRODUCTION

Imagine it is the 1950s. A well-respected European pharmaceutical company develops the first safe sleeping pill—we'll call it "T-Pill." T-Pill is seen as an extremely successful medicine for treating pregnant women with morning sickness.¹ It is licensed as a prescription-free over-the-counter drug in most of Europe.² Use of T-Pill is so widespread that in some European countries it becomes "almost as popular as aspirin."³ But T-Pill is silently deadly.

On Christmas Day 1956, the first known victim of T-Pill is born—a little girl without ears.⁴ She is the daughter of a T-Pill Pharmaceutical Company employee.⁵ Over time, thousands of children around the world are born with severe physical disabilities "including flipper-like arms and legs."⁶ Some of these children are institutionalized; others have "their flippers amputated to accommodate prostheses for arms and legs."⁷ In one severe case, a mother and her doctor were charged with killing a deformed infant, an act that they saw as merciful.⁸

This horror was real, and its name was thalidomide.⁹ Thanks to the work of a young Food and Drug Administration (FDA) pharmacologist, thalidomide never reached the United States, and in 1962, it was banned worldwide.¹⁰ However, the way that thalidomide reached the market underscores a real issue that still persists today. Thalidomide was never tested on pregnant animals.¹¹ Thus, its effects on pregnant women were unknown and thousands of families suffered.¹² Although thalidomide led to stricter regulatory reforms for the United States pharmaceutical industry, reform efforts to ensure that drugs are tested on women and men at parity are still developing.¹³ Thalidomide is "one of the darkest episodes in pharmaceutical research

1. Michael Winerip, *The Death and Afterlife of Thalidomide*, N.Y. TIMES (Sept. 23, 2013), http://www.nytimes.com/2013/09/23/booming/the-death-and-afterlife-of-thalidomide.html?_r=0 [<http://perma.cc/SL86-V2TX>].

2. *Thalidomide*, SCIENCE MUSEUM, <http://www.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide.aspx> [<http://perma.cc/56BU-K549>].

3. Winerip, *supra* note 1.

4. *Id.*

5. *Id.*

6. *Id.*

7. *Id.*

8. *Id.*

9. Winerip, *supra* note 1.

10. *Id.*

11. *Thalidomide*, *supra* note 2.

12. *Id.*

13. *See* Winerip, *supra* note 1.

history,” and an example of how important it is to test drugs on both men and women.¹⁴

Men and women are not equal. For every male with rheumatoid arthritis there are two to three females.¹⁵ For every girl with autism spectrum disorder there are five boys.¹⁶ For every man with lupus there are six women.¹⁷ The sexes react differently to illness as well. For example, men with dilated cardiomyopathy—weakened and enlarged heart muscle—die at a much younger age than women with the same disease.¹⁸ At the cellular level and in the face of disease, men and women are not equal.¹⁹

For decades, the biomedical community has acted under the assumption that the cellular difference between “XX” and “XY” chromosomes only affects the reproductive tracts of the human body.²⁰ Under this bias, all differences between the sexes, outside of the reproductive tract, must stem from “sex hormones.”²¹ In short, scientists conduct research as if “females are simply a variation on [the male] theme.”²²

This Note will discuss how we can ameliorate the underrepresentation of women in privately owned pharmaceutical company-funded early phase clinical trials.²³ Specifically, where is the margin for pharmaceutical companies to increase their profits by including more women in early phase clinical trials? How does the government take advantage of that “money left on the table” to encourage the desired results?²⁴

14. *Thalidomide*, *supra* note 2.

15. David Page, *Why Sex Really Matters: David Page at TEDxBeaconStreet*, YOUTUBE at 8:42 (Jan. 11, 2013), <https://www.youtube.com/watch?v=nQcgD5DpVlQ> [<http://perma.cc/M74M-D2L6>].

16. *Id.* at 9:16.

17. *Id.* at 9:45.

18. *Id.* at 10:23.

19. *Id.* at 13:59.

20. *See id.* at 14:03.

21. Page, *supra* note 15, at 14:52.

22. Roni Caryn Rabin, *Labs Are Told to Start Including a Neglected Variable: Females*, N.Y. TIMES (May 14, 2014), <http://www.nytimes.com/2014/05/15/health/nih-tells-researchers-to-end-sex-bias-in-early-studies.html> [<http://perma.cc/9UP9-XR9C>]; *see* Page, *supra* note 15, at 16:23 (finding that some researchers do not even know if they are studying XX or XY cell lines, making it impossible to account for the fundamental differences between male and female cells).

23. It is important to note that the issue of gender bias in medical research begins with the selection of male cell lines and male animals for research. However this Note will focus only on women in privately funded clinical trials.

24. This Note makes two assumptions. One, if there were a profit margin for private pharmaceutical companies to make money off of including women in early phase clinical trials, they would have done so. Two, “historical bias” against women in clinical trials,

Assuming that the underrepresentation of women in privately funded clinical trials is a supply side issue, and not an irrational bias, this Note identifies two possible solutions. One, insulate private pharmaceutical companies against the extreme liability they fear from damaging a woman's ability to reproduce. Two, incentivize pharmaceutical companies to market and pay more women to participate in early stage clinical trials. The goal of such solutions is to have sex viewed as a mere biological variable for the purposes of clinical trials.

I. A BRIEF HISTORY OF WOMEN IN CLINICAL TRIALS

A. *Introduction to Drug Development*

Today, the Food and Drug Administration oversees the process by which new drugs are tested and approved for marketing in the United States.²⁵ New drugs are subject to laboratory tests before they are tested for human safety, including appropriate dosage and effectiveness.²⁶ Clinical trials are the studies conducted on humans, they process through three phases.²⁷ Phase I is small-scale testing in a minimal number of "healthy volunteers at low doses to establish minimal safety."²⁸ Phase II is medium-scale testing in targeted diseased volunteers "treated to establish a safe and possibly efficacious dose."²⁹ Phase III is "large-scale testing in hundreds to thousands of patients suffering" from the targeted disease to prove that the drug has the desired effect.³⁰

1. *History of Women and Drug Development*

Historically, women have been excluded from early phase clinical trials (Phases I and II).³¹ The earliest attempts to regulate pharmaceutical testing, manufacturing, and marketing "ignored sex

while pertinent and real, is the retrospective answer to this problem, whereas this Note seeks a prospective answer.

25. Cynthia Hathaway, *A Patent Extension Proposal to End the Underrepresentation of Women in Clinical Trials and Secure Meaningful Drug Guidance for Women*, 67 FOOD & DRUG L.J. 143, 145 (2012).

26. *Id.*

27. *Id.*

28. *Id.*

29. *Id.*

30. *Id.*

31. Ellen Pinnow et al., *Increasing Participation of Women in Early Phase Clinical Trials Approved by the FDA*, 19 WOMEN'S HEALTH ISSUES 89, 89 (2009).

entirely.”³² Before 1938, drug laws did not require safety testing; that changed with the implementation of the Food, Drug, and Cosmetics Act, “passed in response to [the] widely-publicized contamination of . . . ‘Elixir Sulfanilamide,’ which caused the deaths of over 100 people, mostly children”³³

In the 1960s, thalidomide, and its teratogenic³⁴ effects on fetuses,³⁵ caused the U.S. Food and Drug Administration (FDA) to examine its protocols governing the inclusion of “females of child bearing potential” in clinical trials.³⁶ Thalidomide was a drug primarily prescribed as a sedative and later used to alleviate nausea and morning sickness in pregnant women; however, it led to severe fetal deformities, primarily phocomelia (malformation of the limbs).³⁷

In 1977, the FDA issued the “General Considerations for the Clinical Evaluation of Drugs,” which prohibited females of childbearing potential from participating in Phase I and early Phase II clinical trials.³⁸ Only after early Phase II trials showed the effectiveness of a drug in men and/or older women could fertile females be included.³⁹

2. The 1980s and the Tipping Point

In the 1980s, mainstream medicine began to take greater notice of women’s health issues.⁴⁰ Several large and influential studies had “omitted women as subjects of medical research.”⁴¹ “[T]he first study of the role of estrogen in preventing heart disease was conducted

32. Hathaway, *supra* note 25, at 145.

33. *Id.*

34. Teratogenic means congenital malformations in fetuses.

35. It is interesting to note that a female FDA inspector, Frances Kelsey, prevented thalidomide’s approval within the U.S. over the objections of her supervisors and pharmaceutical companies. Kelsey was concerned about the lack of data indicating “whether the drug could cross the placenta, which provides nourishment to the fetus.” See Bara Fintel et al., *The Thalidomide Tragedy: Lessons for Drug Safety and Regulation*, HELIX (July 28, 2009), <https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation> [<http://perma.cc/5HMP-6W4Z>]; see also, e.g., Billy Joel, *We Didn’t Start the Fire*, BILLYJOEL.COM (Sept. 21, 1989), <http://www.billyjoel.com/music/storm-front-we-didnt-start-fire> [<http://perma.cc/6LRB-QAKS>] (referencing the “children of thalidomide” in his song *We Didn’t Start the Fire*, which demonstrated the cultural penetration the negative effects of thalidomide had on a generation).

36. Pinnow et al., *supra* note 31, at 89.

37. Fintel et al., *supra* note 35.

38. Pinnow et al., *supra* note 31, at 89.

39. *Id.*

40. Londa Schiebinger, *Women’s Health and Clinical Trials*, 112 J. CLIN. INVEST. 973, 973 (2003), <http://www.jci.org/articles/view/19993> [<http://perma.cc/KX9Q-WSA7>].

41. *Id.*

solely on men”⁴² The Physicians’ Health Study of the effects of aspirin on cardiovascular disease enrolled 22,071 men and 0 women.⁴³ The Multiple Risk Factor Intervention Trial, a randomized study from 1973 to 1982 evaluating the correlation between blood pressure, smoking, cholesterol, and coronary heart disease enrolled 12,866 men and 0 women.⁴⁴ The National Institute on Aging’s Baltimore Longitudinal Study of Aging, a long range study conducted from 1958 to 1975, excluded women despite the fact that women accounted for “two-thirds of the population over age 65.”⁴⁵ However, not all women’s health issues were ignored. For example, the Framingham Heart Study, started in 1948, enrolled “slightly more women than men” and “has long stood as the benchmark epidemiological study on cardiovascular health”⁴⁶

The tipping point began with the AIDS epidemic of the 1980s, which brought to light the sidelining of women, specifically the “lack of women’s access to experimental AIDS medicines.”⁴⁷ “Despite overwhelming evidence since the first year in which AIDS was reported that the disease affected both genders . . . research on AIDS was initially limited to investigations with men.”⁴⁸ As late as 1987, health officials “claimed that there were insufficient numbers of infected women to devote scarce resources to studying the epidemic in women . . . [although] women compromised 50% of AIDS cases in Africa and AIDS had become the eighth leading cause of death in American women aged 15–44.”⁴⁹ “[W]omen’s access to experimental medicines was [also] severely limited”⁵⁰ The clinical trial of AZT illustrates the access problem. “When the FDA approved AZT in 1987 . . . only four percent of the participants were female, [and] not one of the 63 federally-sponsored studies had analyzed its effects on women.”⁵¹ Unsurprisingly, “women suffered disproportionately from toxic side effects.”⁵²

42. *Id.*

43. *Id.*

44. *Id.*

45. *Id.*

46. Schiebinger, *supra* note 40, at 973.

47. Hathaway, *supra* note 25, at 147.

48. *Id.* (quoting Ruth Faden et al., *Women as Vessels and Vectors: Lessons from the HIV Epidemic*, in *FEMINISM & BIOETHICS: BEYOND REPRODUCTION* 252, 254 (Susan M. Wolf ed., 1996) (discussing the health ramifications of excluding women from AIDS trials)).

49. *Id.* at 148–49.

50. *Id.* at 148.

51. *Id.* (alteration in original).

52. *Id.*

“Until 1998 . . . the FDA . . . routinely conducted [clinical trials of new drugs] predominately on men . . . even though women consume approximately 80% of pharmaceuticals in the U.S.”⁵³ In 1987, the National Institutes of Health (NIH) updated its grant guidelines to encourage “scientists seeking funding to include women and minorities in their clinical research.”⁵⁴ However, a 1992 survey by the U.S. General Accounting Office found that fewer than half of prescription drugs on the market “had been analyzed for sex-related response differences.”⁵⁵

1993 saw the inauguration of the first large-scale study of women’s health. The Women’s Health Initiative⁵⁶ was “a fifteen-year, \$625 million study . . . involv[ing] more than 160,000 female subjects.”⁵⁷ That same year, “President Clinton signed an NIH appropriations bill that codified as statute several policies supporting” women as both subjects and investigators.⁵⁸ Finally, the FDA “issued proposed new regulations that revise[d] its guidelines for the drug development process in favor of the inclusion of women.”⁵⁹

B. The Current Medical Regulatory Climate

As helpful as the regulatory improvements since the 1960s have been to expanding the inclusion of women in clinical trials, they still fall short of gender equality. “Women now make up more than half [of] the participants in” publicly funded clinical research, but are often still “underrepresented in clinical trials carried out by [private] drug companies and medical device manufacturers.”⁶⁰ “As a

53. Schiebinger, *supra* note 40, at 973.

54. Cari Romm, *Where Are All the Female Test Subjects?*, THE ATLANTIC (Sept. 4, 2014), <http://www.theatlantic.com/health/archive/2014/09/where-are-all-the-female-test-subjects/379641> [<http://perma.cc/TWX8-4JDL>].

55. Schiebinger, *supra* note 40, at 973–74.

56. The National Institutes of Health Revitalization Act of 1993, Subtitle B—Clinical Research Equity Regarding Women and Minorities, established various women’s health protections. Section 492B(a)(1)(A) required inclusion of women, section 486(a) established an Office of Research on Women’s Health, section 486A established the National Data System and Clearinghouse on Research on Women’s Health, and section 486(b)(9) required a biennial report. National Institutes of Health Revitalization Act of 1993, Subtitle B (1993) (codified as amended at part G of title IV of the Public Health Service Act, 42 U.S.C. § 201 et seq.), <http://orwh.od.nih.gov/about/pdf/NIH-Revitalization-Act-1993.pdf> [<http://perma.cc/E69G-D9X3>].

57. Vanessa Merton, *The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. Women) from Biomedical Research*, 3 TEX. J. WOMEN & L. 307, 312 (1994).

58. *Id.*

59. *Id.* at 312–13 (internal citation omitted).

60. Rabin, *supra* note 22.

result of the over-reliance on male animals and male cell lines . . . '[w]e literally know less about every aspect of female biology compared to male biology.'"⁶¹

Studies utilizing government funding tend to include a higher number of female participants—"41%, compared with 37% for studies not receiving government funding."⁶² However, this data does not take into account the rate at which women participate in the different phases of clinical trials. A review of New Molecular Entities approved by the Center for Drug Evaluation and Research between 2000 and 2002 found that "[w]omen represented only 24% of all participants in [Phase I and Phase II of clinical trials], compared with 64% [of] men"⁶³ Equally problematic, "12% of trials did not specify the sex of participants."⁶⁴ A Government Accountability Office (GAO) report from 2011 concluded that women were underrepresented in Phase I trials, as they accounted for only "22% of participants in the initial safety trials used to set dosing levels."⁶⁵

The FDA has also recently taken steps to increase transparency surrounding women and minorities in clinical trials. Among these steps is the development of the pilot program entitled Drug Trials Snapshots, which provides information to the public about who participated in clinical trials for new FDA approved drugs.⁶⁶ Six new drugs currently comprise the snapshot.⁶⁷ All were approved between May 8, 2014, and June 20, 2014.⁶⁸ They treat a variety of afflictions including serious bacterial infections, including Crohn's Disease, Ulcerative Colitis, fungal infections, and peripheral arterial disease related to heart attacks.⁶⁹ The Snapshot breakdowns include the drug's use, benefits, a demographic portrait of the clinical trials, and differences between sex, race, and age broken out by efficacy.⁷⁰

61. Roni Caryn Rabin, *Health Researchers Will Get \$10.1 Million to Counter Gender Bias in Studies*, N.Y. TIMES (Sept. 23, 2014), <http://www.nytimes.com/2014/09/23/health/23gender.html> [<http://perma.cc/52FV-J43C>].

62. Nicola Jones, *Too Few Women in Clinical Trials? Cancer-Drug Studies Fail to Reflect True Incidence of Disease in the Population*, NATURE NEWS (June 8, 2009), <http://www.nature.com/news/2009/090608/full/news.2009.549.html> [<http://perma.cc/8HHD-2NVF>].

63. Pinnow et al., *supra* note 31, at 90.

64. *Id.* (internal citation omitted).

65. *Id.* (internal citation omitted).

66. See *Drug Trials Snapshot*, FOOD & DRUG ADMIN. (Nov. 21, 2014), <http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm> [<http://perma.cc/UZE9-NEJB>].

67. *Id.*

68. *Id.*

69. *Id.*

70. *Id.*

Drug*	Use	Efficacy	Side Effects	Baseline Sex Demographics	Sex Assessment Safety
Dalvance	Treat serious bacterial skin infection	Similarly effective in men and women	Frequency of side effects similar among men and women	M 767 (58%)	F 545 (42%) M 1777 (59%) F 1225 (41%)
Entyvio	Crohn's Disease	Similarly effective in men and women	Frequency of side effects similar among men and women	M 576 (46%)	F 669 (54%) M 1045 (52%) F 965 (48%)
Entyvio	Ulcerative Colitis	Similarly effective in men and women	Frequency of side effects similar among men and women	M 431 (58%)	F 316 (42%) M 1045 (52%) F 965 (48%)
Jublia	Fungal infection	Greater efficacy observed in women than men	Difference in side effects by sex not evaluated	M 1,275 (77%)	F 376 (23%) Difference in side effects by sex not evaluated
Sivextro	Bacterial infection	Similarly effective in men and women	Frequency of side effects similar among men and women	M 841 (63%)	F 492 (37%) M 841 (63%) F 492 (37%)
Zontivity	Peripheral arterial disease	Similarly effective in men and women	Risk of bleeding higher among women than men	M 20,123 (76%)	F 6,326 (24%) M 20,123 (76%) F 6,326 (24%)

* Data distilled from the U.S. Food and Drug Administration Drug Trials Snapshot.⁷¹ (Instances where different efficacy or side effects observed among women and men are highlighted as such.)

71. Drug Trials Snapshot, *supra* note 66.

The Snapshot data seems to indicate that there is variability of sex parity among clinical trials for new molecular entities even among private pharmaceutical companies. It is also important to note that this data does not differentiate between early phase clinical trials and later stage clinical trials.⁷²

The recent media attention surrounding this issue has sparked responses from the regulatory agencies and Congress. On September 23, 2014, the National Institutes of Health announced “that it will distribute \$10.1 million in grants to more than 80 scientists” studying a variety of subjects.⁷³ The funds will be used to include more women in clinical trials, as well as to ensure that laboratory animals and cell lines represent both genders.⁷⁴

Additionally, Representative Jim Cooper (D-Tenn.) and Representative Cynthia Lummis (R-Wyo.) are co-sponsoring a bill—the “Research for All Act of 2015”—to end gender bias in clinical trials.⁷⁵ The bill would apply to federally-funded research and would require that “cells or tissues . . . are derived from both male and female organisms . . . [or] both male and female animals are included as subjects . . . [and] results are disaggregated according to whether the subjects are male or female” so that “safer [and] more effective treatment for males or females” can be provided.⁷⁶ However, both of these solutions fail to change the behavior of the pharmaceutical industrial complex and they fail to provide a targeted solution to the deficit of women in early-stage clinical trials.

C. A Brief Review of Previously Suggested Solutions

An overview of the literature delineates two avenues of proposed solutions to this issue: agency action or judicial action. However, the focus remains on impacting publicly funded research instead of privately funded research. Previously suggested agency based solutions include:

- (1) Altering the 2011 NIH guidelines “encouraging” women as subjects in NIH-funded research to mandate that all clinical trials include women.⁷⁷

72. *See id.*

73. Rabin, *supra* note 61.

74. *Id.*

75. H.R. 2101, 114th Cong. (2015).

76. *Id.* §§ 3, 4(b)(2).

77. Vicki Lawrence MacDougall, *Medical Gender Bias and Managed Care*, 27 OKLA. CITY U. L. REV. 781, 819 (2002).

- (2) Eliminating or narrowly defining the “clear and compelling rationale and justification” exception to the NIH Guidelines.⁷⁸
- (3) Altering the FDA and NIH standards to resemble those of the Department of Health and Human Services (HHS), which provide greater leeway for clinical trials on fertile or pregnant women.⁷⁹
- (4) Increasing the NIH’s budget for “women’s diseases.”⁸⁰ This seems to be the solution contemplated by NIH’s recent \$10.1 million grant to include more women and female animals and cell lines in research.⁸¹
- (5) Enforcing the 1998 FDA amended regulation requiring sponsors to break down drug safety and efficacy data by gender, age, and race.⁸²
- (6) Enforcing the FDA’s guidelines recommending clinical trials include women in numbers sufficient to detect clinically statistical gender differences in drug responses.⁸³
- (7) Incentivizing pharmaceutical companies to include women in their clinical trials through a patent extension, similar to that of the pediatric medical patent extension structure.⁸⁴

Previously suggested judicial solutions run the gambit from personal injury actions to enforcing the principle of self-autonomy.⁸⁵ One option is to pursue suits under 42 U.S.C. section 1985(3), which allows injured parties to recover damages for any conspiracy founded on discriminatory purposes based on the plaintiff’s membership in a class, which deprives that person of equal protection under the law.⁸⁶ One could argue that there is no similar NIH policy to exclude men from clinical trials if the research could injure their reproductive capabilities, even though a man’s reproductive functioning may also

78. *Id.* at 819 (emphasis omitted).

79. *Id.* at 828–29.

80. L. Elizabeth Bowles, *The Disfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap*, 45 VAND. L. REV. 877, 920 (1992).

81. See Rabin, *supra* note 61 and accompanying text.

82. See Investigational New Drug Applications and New Drug Applications, 63 Fed. Reg. 6854 (Aug. 10, 1998) (to be codified at 21 C.F.R. 314.50(d)(5)).

83. Bowles, *supra* note 80, at 891–93.

84. Hathaway, *supra* note 25, at 144.

85. See MacDougall, *supra* note 77, at 792, 823.

86. *Id.* at 789.

be injured in a clinical trial.⁸⁷ However, although a woman may be a member of a class for the purpose of a Section 1985 action, there must still be a conspiracy or discriminatory intent, which would be difficult to demonstrate.⁸⁸

Another option is to challenge the gender bias practices based on a personal injury action.⁸⁹ However, medical negligence is the standard, which is based on the violation of a standard of care customary to the practice of other physicians in the same area of medicine, making it unlikely to succeed since the practice of gender bias in medical research is endemic.⁹⁰ Yet another potential avenue for litigation would arise under the doctrine of informed consent where there is a violation of a doctor's duty to disclose any material risk of treatments or alternatives.⁹¹ However, this argument requires construing the gender gap in clinical trials—and as such the effects it may have on the accuracy of dosage, side effect, and even effectiveness—as a material risk of treatment that must be disclosed.⁹²

An option to attack pharmaceutical companies directly would be founded on a negligence standard or a theory of strict products liability in tort.⁹³ The negligence argument would establish that reasonable care requires a gendered analysis of any clinical trial data “to ascertain any side effect[s] or dosage requirements unique to women.”⁹⁴ The strict liability argument is based on the pharmaceutical companies' failure to provide adequate warning and “injecting a defectively designed product into the stream of commerce.”⁹⁵ Finally, a litigant could argue that the exclusion of women from clinical trials, because they may become pregnant, violates the Supreme Court's established principle of self-autonomy.⁹⁶

II. FACTORS CONTRIBUTING TO GENDER DISPARITY IN CLINICAL TRIALS

The above-explored solutions rely on either targeting publicly funded clinical trials or a theory of punishment to incentivize a change in private-sector pharmaceutical company behavior. Given

87. *Id.* at 821.

88. *Id.* at 789–90.

89. *Id.* at 793.

90. *Id.* at 792.

91. MacDougall, *supra* note 77, at 796.

92. *See id.* at 796–97.

93. *Id.* at 821–22.

94. *Id.* at 822.

95. *Id.* at 822–23.

96. *Id.* at 823.

the recent public outcry over the gender gap in clinical trials and the NIH funding increase earmarked for this cause,⁹⁷ publicly funded clinical trials are already on their way to a solution.

Instead, it is time to concentrate on changing the behavior of “Big Pharma,” a nickname for influential pharmaceutical companies represented by the Pharmaceutical Research and Manufacturers of America (PhRMA).⁹⁸ This targeted approach also stands to produce a larger effect on the overall market because private pharmaceutical company Research and Development (R&D) spending far outstrips NIH funding. In 2009 the total NIH budget was \$30.6 billion.⁹⁹ That same year, the R&D expenditures of *only* PhRMA member companies was \$45.8 billion, which was an abrupt downturn from highs of \$47.9 and \$47.4 billion in the previous two years.¹⁰⁰ Further, the pharmaceutical industrial complex is a multibillion dollar industry,¹⁰¹ with strong lobbying power,¹⁰² and the ability to overturn or impact any restricting rules or statutes, and the war chest to fight any court imposed penalties.¹⁰³ For these reasons, it may take a combined “carrot” and “stick” strategy to impact the behavior of private pharmaceutical funded clinical trials.

A. Gender Equality in Early Phase Clinical Trials for New Molecular Entities

Although this could be framed as a pure equality-of-the-sexes issue, the truth is there is actual harm being done to women’s health from their underrepresentation in clinical trials. The consequence

97. See Rabin, *supra* note 61.

98. “Big Pharma is [a] nickname given to the world’s vast and influential pharmaceutical industry and its trade and lobbying group, the Pharmaceutical Research and Manufacturers of America . . .” Six of the largest drug companies in the world have their headquarters in the United States: Johnson & Johnson, Pfizer, Abbot Laboratories, Merck, Bristol-Myers Squibb, and Eli Lilly. The ten largest drug companies in the world made a net profit of \$429.4 billion in 2014. See *Big Pharma*, DRUGWATCH, <http://www.drugwatch.com/manufacture> [<http://perma.cc/6ZVK-UYU>].

99. *Private and Public R&D Spending*, PhRMA, <http://www.phrma.org/private-public-rd-spending> [<http://perma.cc/9DBH-69X3>].

100. *Id.*

101. *Top 25 Pharma Companies by Global Sales*, PMLIVE, http://www.pmlive.com/top-pharma_list/global_revenues [<http://perma.cc/K78U-NDEF>].

102. See *Annual Lobbying on Pharm/Health Products*, OPENSECRETS.ORG (2015), <http://www.opensecrets.org/lobby/indusclient.php?id=H04> [<http://perma.cc/L4VY-CVGL>].

103. See, e.g., Jef Feeley, *Merck Pays \$23 Million to End Vioxx Drug-Purchase Suits*, BLOOMBERG NEWS (July 19, 2013), <http://www.bloomberg.com/news/articles/2013-07-18/merck-pays-23-million-to-end-vioxx-drug-purchase-suits> [<http://perma.cc/F4NN-9UQ3>]; Peter Loftus & Brent Kendall, *Merck to Pay \$950 Million in Vioxx Settlement*, WALL ST. J. (Nov. 23, 2011), <http://www.wsj.com/articles/SB10001424052970204531404577054472253737682> [<http://perma.cc/Z7MF-BWZ2>].

of early stage underrepresentation is male-only clinical data.¹⁰⁴ This can lead to a variety of complications with treatments, medicine, and medical devices later down the line.¹⁰⁵

As a baseline issue, women are particularly at risk of being prescribed dosages devised for the average male weight and metabolism.¹⁰⁶ For example, acetaminophen (Tylenol) is eliminated by the female body at about 60% the rate of elimination by men.¹⁰⁷ Women are also at approximately two times greater risk for an adverse drug reaction than men,¹⁰⁸ and “experience more severe side effects from new treatments”¹⁰⁹ In 2013, the FDA told women to cut their doses for the sleeping pill Ambien in half, because new studies showed that women “metabolize the active ingredient more slowly than men do.”¹¹⁰

Equally problematic are the studies that do not report results for men and women separately.¹¹¹ Research lags for treatment of heart disease, “the number one killer of women . . . because women make up only one-third of the participants in [the] clinical trials . . . and most of [the] studies don’t report results for [the sexes] separately.”¹¹² Women are also less likely to enroll in studies; for example women who do not smoke are three times more likely than non-smoking men to get lung cancer, but women are less likely to enroll in lung-cancer studies.¹¹³

The problem also extends to biomedical devices. For instance, the FDA approved an implantable defibrillator for both sexes even

104. Even before the clinical trial stage, the cell lines experimented on are gendered. Each cell line has its own sex, “and that genetic difference results in different biochemical processes within those cells.” For example, neurons cultured from males are more susceptible to death from starvation than those from females, because of differences in the way cells process nutrients. Rabin, *supra* note 22.

105. See Bowles, *supra* note 80, at 886.

106. Schiebinger, *supra* note 40, at 974.

107. *Id.*

108. *Id.* (“For example, some antithrombotic agents used to break up blood clots immediately after a heart attack, while beneficial to many men, may cause significant bleeding problems in women. Commonly prescribed drugs used to treat high blood pressure tend to lower men’s mortality from heart attack but have been shown to increase cardiac-related deaths among women. Emerging evidence also suggests that the effects of antidepressants can vary over the course of the menstrual cycle. Subsequently, drug dosage may be too high at some points during estrous and too low at others.”) (citations omitted).

109. Rabin, *supra* note 22.

110. *Id.*

111. Deborah Kotz, *Medical Research Still Lags on Women, Study Says*, BOSTON GLOBE (Mar. 3, 2014), <https://www.bostonglobe.com/lifestyle/health-wellness/2014/03/03/research-lacking-gender-differences-disease-study-finds/HV1QWeYEm8J1Lu6KTrIW1H/story.html> [http://perma.cc/J2RD-QG7S].

112. *Id.*

113. See *id.*

though women only accounted for 15% of the participants in the 2002 effectiveness study.¹¹⁴ A subsequent 2009 study found that there was no benefit for women.¹¹⁵ Cancer studies are another area of concern, with 75% of cancer studies underrepresenting women.¹¹⁶ For example, 45% of lung cancer diagnoses are in women, but on average only 31% of lung cancer study participants are women.¹¹⁷ Overall, women are materially affected in their health by the absence of gender parity in clinical trials for new treatments.

B. Supply Side Problem: Why Are Women Risk Adverse to Joining New Molecular Entity Clinical Trials?

The typical argument against the inclusion of women in clinical trials, is that it is difficult to recruit women for such trials.¹¹⁸ Reasons given for this difficulty are often sociological. Women are frequently the principal caregivers for children, the disabled, family, and friends, and have less mobility and time to take off to attend to their own medical needs.¹¹⁹ Women are more likely to have to account to a male partner for their time, and their “disadvantaged economic position means they have less to spend on transportation” to and from a clinical trial.¹²⁰ In the substance abuse program context, women’s participation increased dramatically in response to childcare facilities being provided as part of the program.¹²¹ In the AIDS context, studies did not reimburse for travel time or childcare, and pregnant women were required to get permission from the fetus’s father before enrolling in the clinical trial.¹²² Another issue may be that men and women react differently to the risk-benefit analysis posited by participating in a clinical trial.¹²³

If the supply-side issue is caused by the structural nature of the vast majority of female roles played in society, than one solution is to subsidize pharmaceutical company recruiting costs so that burden

114. *Id.*

115. *Id.*

116. Jones, *supra* note 62.

117. *Id.*

118. See Merton, *supra* note 57, at 315; Symposium, *Women’s Health Law Symposium*, 16 WOMEN’S RTS. L. REP. 17, 18 (1994).

119. Merton, *supra* note 57, at 315; see Jones, *supra* note 62.

120. Merton, *supra* note 57, at 315.

121. *Id.* at 315.

122. LESLIE LAURENCE & BETH WEINHOUSE, OUTRAGEOUS PRACTICES: THE ALARMING TRUTH ABOUT HOW MEDICINE MISTREATS WOMEN 61, 150 (1994).

123. Jones, *supra* note 62.

is taken from their bottom line. As I will discuss later, this incentivizing “bribe” may take a few different forms. If the supply-side issue is caused by a gendered presentation to risk-benefit analysis, then to impact feminine behavior, we must examine the cause of the risk differential. There are three options for risk presentation: (1) the sexes have no difference in risk appetite, (2) the sexes value risk differently, or (3) the sexes perceive risk differently.

1. No Difference in Risk Appetite

If the physical risk of participating in an early stage clinical trial for a new molecular entity—e.g., a complete unknown—is *actually greater*¹²⁴ for women than men, then there is no actual difference in risk appetite. Thus, it is rational for women to have lower rates of participation in clinical trials, and there is no way to move their position, short of mandating participation or paying women to take more risk.¹²⁵

The only reason to mandate participation is if we, as a society, think that the cost of having fewer women in clinical trials outweighs the price of mandating individual women to take that risk. A mandate could take the form of instituting a randomized “draft” to force the politically agreed upon percentage of women to participate in early stage clinical trials regardless of the risk, similar to what we previously did with the military. However, the political will to achieve such a mandate is unlikely.¹²⁶ Additionally, a mandate would face a Free Rider Problem; that is, it is collectively in “*women’s*” best interest to have pharmaceutical products that are appropriate for feminine treatment, but it is in no individual *woman’s* best interest to take the risk. To put it colloquially, no one will want to bite the bullet.

2. Valuation Difference in Risk Appetite

Under this hypothesis, the physical risk is the same to women and men participating in early stage clinical trials, but women value their reproductive ability more than men. There is some evidence that women do value their reproductive ability more than men as a biological strategy for mating, “[b]ecause women and not men bear the time- and energy-intensive burden of gestation, parturition, and

124. The risk would actually be greater if all other variables being equal, a woman or her reproductive capability will be injured more times than a man in the same clinical trial.

125. Paying individual women to take higher risks would most likely run afoul of collective bargaining regulations.

126. See Merton, *supra* note 57, at 380–81.

lactation, more of their value as potential spouses is tied up in their reproductive capacity.”¹²⁷

3. Perceived Difference in Risk Appetite

Under this hypothesis, the risk is the same in women and men, but women perceive a higher risk of participating in clinical trials, possibly because it is more salient to them as the sex that carries children. Numerous studies have found a perceived risk differential between men and women specifically in the health and environmental fields.¹²⁸ “[W]omen are found to perceive themselves . . . as being more susceptible [to meningococcal diseases], and therefore perceive a higher risk associated with the stated diseases.”¹²⁹ However, risk perception cannot be reduced to a simple gender binary. Gender, race, income, education level, and marital status all play a role in risk perception.¹³⁰

In a 1998 study by Jianakopulos and Bernasek, females were found to be more risk adverse than males, while single black females were found to hold riskier assets than single white women.¹³¹ A 2001 study by Bernasek and Shwiff found that among married women, if a male spouse becomes more “risk loving,” then the female partner becomes more “risk averse.”¹³² A 1996 study by Davidson and Freudenburg found that “women show higher concern for risks associated with health and safety of the family and site-specific environmental issues. Women were found to be less trusting of institutions and technology that surround the origins of potential risk.”¹³³

Further complicating the picture, studies tend to show that white men also perceive less risk. A 1999 study by Slovic suggests that:

perhaps white males see less risk in the world because they create, manage, control, and benefit from so much of it. Perhaps women and nonwhite males see the world as more dangerous because in many ways they are more vulnerable, because they

127. SATISFACTION IN CLOSE RELATIONSHIPS 11 (Robert J. Sternberg & Mahzad Hojjat eds., 1997).

128. See Chian Jones Ritten, *Measuring Values for Environmental Public Goods: Incorporating Gender and Ethnic Social Effects Into Stated-Preference Value-Elicitation Methods* (2011) (unpublished Ph.D. dissertation, Colo. State University), <http://dspace.library.colostate.edu/browse?type=author&value=Jones+Ritten%2C+Chian> [<http://perma.cc/6YYW-HL4G>].

129. *Id.* at 129.

130. *Id.* at 38.

131. *Id.* at 28.

132. *Id.*

133. *Id.* at 33.

benefit less from many of its technologies and institutions, and because they have less power and control¹³⁴

Importantly, a 1997 study by Bord and O'Conner showed that women who perceive more risk are also "willing to take voluntary actions to protect themselves against sources of perceived risks."¹³⁵

In its Survey of U.S. Adults on Clinical Trials Research Participation, the Society for Women's Health Research found that women were more likely to be hesitant to participate because of concerns over the type of study, the risk, and their valuation of their own health.¹³⁶ For example, 21.7% of women, as compared to 15.4% of men, would hesitate to participate depending on the type of study.¹³⁷ Whereas, 17.5% of women, as compared to 15.2% of men, would be hesitant to participate because of risky or dangerous side effects, which suggests a higher perception of risk.¹³⁸ More women—9.7% as compared to 5.1% of men—thought that they were not healthy enough to participate in a clinical trial.¹³⁹ Additionally, more women—7.2% as compared to 2.4% of men—thought they were too old to participate.¹⁴⁰ Interestingly, more men than women said they did not have the time to participate—26.7% compared to 17.4%¹⁴¹—but this could merely reflect men putting a higher premium on their time.

In sum, it is important to keep in mind that women are behaving rationally in response to a risk-benefit analysis when crafting solutions to this issue.

III. LITIGATION SOLUTIONS

Two potential litigation-based solutions to change the behavior of pharmaceutical companies are (1) pre-empt state tort law with regard to teratogenic risks and (2) enact a statute giving non-governmental organizations (NGOs) standing to sue pharmaceutical companies on behalf of women for not complying with statutory requirements.

134. Ritten, *supra* note 128, at 36.

135. *Id.* at 38.

136. SOC'Y FOR WOMEN'S HEALTH RESEARCH, *Survey of U.S. Adults on Clinical Trials Research Participation 2* (2008), http://swhr-web.s3.amazonaws.com/migrated/WomensHealthWeekSurveyResults.pdf%3FdocID=2041_53bddd60976d57.14058554.pdf%3FdocID=2041 [<http://perma.cc/ZDV9-XTB9>].

137. *Id.*

138. *Id.*

139. *Id.*

140. *Id.*

141. *Id.*

A. The Assumption of Risk Clause from Hell

To achieve parity of women in early phase clinical trials, pharmaceutical companies must be incentivized to take on the perceived risk of including more women, who may be likely to sue over bad outcomes, specifically teratogenic risks.¹⁴² However, any incentive structure that walls women off from ex post damages may discourage them from signing up for clinical trials in the first place.

A strategy pre-empting state law regarding teratogenic risks could be constructed similar to the National Childhood Vaccine Injury Act of 1986.¹⁴³ The Act was designed to shield pharmaceutical companies from vaccine liability, specifically from lawsuits by parents claiming that vaccines harmed their children.¹⁴⁴ The Act addressed a shortage of vaccines, triggered by costly tort actions against the manufacturers, by setting up “a no-fault, nontort compensation alternative for individuals injured by compulsory childhood immunization.”¹⁴⁵

In *Bruesewitz v. Wyeth LLC*, the Supreme Court upheld the Act in a 6 to 2 ruling.¹⁴⁶ The majority held that Congress found the system necessary to ensure that vaccines remained readily available and to put federal regulators in the best position to decide whether vaccines are safe and properly designed.¹⁴⁷ Justice Scalia opined that the Act “reflects a sensible choice to leave complex epidemiological judgments about vaccine design to the FDA and the National Vaccine Program rather than juries.”¹⁴⁸ The Act also sets up a special tribunal—“The Vaccine Court”—to allow parents compensation for negative side effects that, in the rare instance, accompany vaccination.¹⁴⁹

A similar legislative action could protect pharmaceutical companies from tort suits initiated by women participating in clinical trials in response to teratogenic injuries to fetuses affected by those early stage clinical trials. This would reduce the perceived cost to pharmaceutical companies and expand their profit margin on clinical trials where they have included women at parity with men. The statute could be structured such that the tort protection is not triggered unless there is gender equality at all stages of the clinical

142. MacDougall, *supra* note 77, at 786.

143. 42 U.S.C. §§ 300aa-10 to -33 (West 1987). *But see* 42 U.S.C. § 300aa-18 (repealed 1987).

144. *See* Mary Beth Neraas, Comment, *The National Childhood Vaccine Injury Act of 1986: A Solution to the Vaccine Liability Crisis?*, 63 WASH. L. REV. 149, 149 (1988).

145. *Id.* at 149–50.

146. *Bruesewitz v. Wyeth LLC*, 131 S. Ct. 1068, 1071–72 (2011).

147. *See id.* at 1073.

148. *Id.* at 1080.

149. *See id.* at 1073, 1100.

trials and the data for both sexes is reported to the FDA during their Prescription Drug User Fee Act (PDUFA) filing.¹⁵⁰

However, the inability to receive post hoc compensation for participating in a clinical trial, which results in fetal injuries, could discourage women from participating in such studies. Depending on the profit margin created by removing this liability hanging over pharmaceutical companies, individual companies may be able to counter the disincentive created in the pool of women willing to sign up for clinical trials simply by paying them more.¹⁵¹ However, given the evidence that women perceive greater risk and are thus more risk-averse to early stage clinical trials and other factors impacting their health, the amount of money the pharmaceutical companies may have to pay in marketing and in direct participation subsidies to women may be more expensive than the losses the litigation shield prevents.

B. *Qui Tam Standing Statute*

Enacting a *qui tam* statute is a second option to incentivize pharmaceutical companies to craft gender parity into their early phase clinical trials. This option, unlike the assumption of risk clause, would provide less of a deterrence to already risk-averse women because it preserves the possibility of ex post damages recovery for adverse effects.

Under a *qui tam* statute, Congress could pass a federal statute that gives standing to NGOs in order to sue private pharmaceutical companies in the name of the United States on behalf of women excluded from clinical trials.¹⁵² “*Qui tam*” represents the Latin phrase *qui tam pro domino rege quam pro si ipse in hoc parte sequitur*, which means he “[w]ho sues on behalf of the King as well as for himself.”¹⁵³

The False Claims Act *qui tam* provision¹⁵⁴ provides a model for this proposed gender parity in clinical trials *qui tam* act. The False Claims Act is the “government’s principal antifraud tool.”¹⁵⁵ A gender parity *qui tam* statute could provide the same monitoring function for pharmaceutical company clinical trials and could even extend to genetic line and animal testing.

150. See *infra* notes 183–89.

151. See SOC’Y FOR WOMEN’S HEALTH RESEARCH, *supra* note 136, at 2.

152. See, e.g., Evan Caminker, Comment, *The Constitutionality of Qui Tam Actions*, 99 YALE L.J. 341, 341 (1989).

153. BLACK’S LAW DICTIONARY 1251(6th ed. 1990).

154. 31 U.S.C. §§ 3729–3733 (2015).

155. David Farber, Note, *Agency Costs and the False Claims Act*, 83 FORDHAM L. REV. 219, 223 (2014).

A *qui tam* statute could be constructed to impose civil liability on pharmaceutical companies that do not meet a certain parity of gender in their clinical trials from Phase I through III and/or do not include that gendered data in their PDUFA filings. The statute could be constructed narrowly to give standing to only certain organizations, such as not-for-profit, non-governmental entities involved in health care policy. The *qui tam* framework has the advantage of enlisting the knowledge and resources of the citizens to supplement public law enforcement efforts.¹⁵⁶ However, considering the strength of the pharmaceutical lobby, a statute imposing such broad liability is unlikely to pass.¹⁵⁷

An additional problem with enacting a gender parity *qui tam* statute is that *qui tam* statutes in general are vulnerable to nuisance settlements.¹⁵⁸ A litigant can “employ a nuisance-value strategy” by asserting a “meritless claim . . . in order to extract a payoff based on the cost the other party would incur”¹⁵⁹ Pharmaceutical companies, with their large revenues, would present an attractive target for nuisance suits.

IV. ECONOMIC INCENTIVE SOLUTIONS

Beyond litigation based solutions, economic incentives provide a model for encouraging private pharmaceutical companies to conduct clinical trials to a certain standard of gender parity as set by the FDA. In order to economically affect private pharmaceutical company behavior, there must be “money left on the table” that the government can offer to increase the profit margin and thus affect change.¹⁶⁰ Possible solutions include: (1) establishing a patent extension on the life of new molecular entities which fit the established criteria; and (2) changing the structure of transactional costs for PDUFA filings with the FDA.

156. Caminker, *supra* note 152, at 341.

157. In 2014, the pharmaceutical lobby spent \$229,124,563 on lobbying. This is down from an industry high, since tracking began in 1998, of \$273,009,917 in 2009. The pharmaceutical lobbying industry is large in scale as well, with 357 clients and 1,425 lobbyists as of 2014. Of those lobbyists, 880 (61.1%) are considered “revolvers”—individuals whose professional experience includes positions in both the public and private sector, who thus can leverage the power and access afforded them due to those ties for the pharmaceutical lobby’s interests. See *Industry Profile: Summary, 2009*, OPENSECRETS.ORG, <https://www.opensecrets.org/lobby/indusclient.php?id=H0R&year=2009> [http://perma.cc/9BMN-LR9E]; *Industry Profile: Summary, 2014*, OPENSECRETS.ORG, <https://www.opensecrets.org/lobby/indusclient.php?id=H04&year=2014#> [http://perma.cc/5YDY-9954].

158. Randy J. Kozel & David Rosenberg, *Solving the Nuisance-Value Settlement Problem: Mandatory Summary Judgment*, 90 VA. L. REV. 1849, 1850 (2004).

159. *Id.* at 1850.

160. See Hathaway, *supra* note 25, at 144.

A. Patent Extension

Under Article I, Section 8, clause 8 of the U.S. Constitution, Congress shall have power “[t]o promote the Progress of . . . [the] useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their . . . Discoveries [sic].”¹⁶¹ A patent is issued by the federal government to the first inventor, giving him/her the right to exclude others from “making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States.”¹⁶² The patent grant is limited to twenty years from filing an application for a patent.¹⁶³ However, this twenty-year grant is abrogated by the fact that the drug cannot be marketed for profit until approved by the FDA.¹⁶⁴ Undergoing the process of pre-clinical testing, investigational new drug applications, Phase I studies, clinical and Phase II and III trials, takes years, and requesting approval to market the drug typically itself takes fifteen months.¹⁶⁵ This arduous process shortens the time a manufacturer can take advantage of exclusive marketing in order to recoup its investment.

Two Acts, the 1984 Hatch-Waxman Act,¹⁶⁶ and the 1997 Food and Drug Administration Modernization Act,¹⁶⁷ provide a model for extending patent exclusivity in exchange for drug manufacturers including women at parity in cell line testing, animal testing, and all three phases of clinical trials. The Drug Price Competition and Patent Term Restoration Act of 1984, otherwise known as the Hatch-Waxman Act, amended drug and patent laws to create patent term restoration.¹⁶⁸ Hatch-Waxman provides a patent holder with the entitlement to have a period of time added back to the patent term equal to one-half of the period between the Investigation New Drug Application (IND)¹⁶⁹

161. U.S. CONST. art. I, § 8, cl. 8.

162. 35 U.S.C. § 154(a)(1) (2006).

163. *Id.*

164. See JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 17 (2005).

165. Hathaway, *supra* note 25, at 168.

166. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.); see Hathaway, *supra* note 25, at 168.

167. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

168. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.).

169. An IND is an Investigation New Drug Application, which is filed with the FDA to conduct human testing. The IND also submits preclinical data about the new compound, its formulation, and effect in animals. The IND also contains information about plans to test the safety of the compound in Phase I studies. See Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 192 (1999).

and a New Drug Application (NDA)¹⁷⁰ submission, plus the entire NDA review period.¹⁷¹ However, the total period restored cannot exceed five years and the total term of the restored patent cannot exceed fourteen years.¹⁷² Hatch-Waxman amendments also provide marketing exclusivity periods for new chemical entities,¹⁷³ orphan drugs,¹⁷⁴ and pediatric studies.¹⁷⁵

The 1997 Food and Drug Administration Modernization Act (FDAMA) established an additional six-month exclusivity period for studies done on children.¹⁷⁶ The purpose of the pediatric exclusivity was to improve pediatric labeling of drugs to correct a lack of adequate dosing, safety, and efficacy data because children are traditionally excluded from the drug development process.¹⁷⁷ FDAMA was re-authorized in 2002 and is one of the most successful federal initiatives for children's health.¹⁷⁸ Whereas only eleven pediatric studies were conducted in the six years before the FDAMA was enacted, 191 were proposed in the first three years after the Act went into effect.¹⁷⁹

Although the pediatric patent extension is a good model to apply to the problem of incentivizing pharmaceutical companies to create gender parity in drug development, the FDAMA process is voluntary on both sides.¹⁸⁰ Additionally, a mere six-month extension for potentially more expensive changes affecting every level of the drug development process from cell lines through Phase III human clinical trials may be too little to compensate drug developers for their effort.¹⁸¹ A

170. An NDA requests approval to market a drug. Review typically takes approximately fifteen months. *Id.*

171. 35 U.S.C. § 156(c) (2006).

172. THOMAS, *supra* note 164, at 17.

173. *Id.* at 348.

174. Orphan drugs are drugs that treat rare diseases and are thus very expensive. To qualify for orphan drug status a drug must treat a rare disease which affects fewer than 200,000 people in the United States or affects more than 200,000 persons living in the United States but for which there is no reasonable expectation that sales would recover the costs of development. An orphan drug is exclusive for seven years. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended in scattered sections of 21 and 42 U.S.C.); see *Developing Products for Rare Diseases & Conditions*, FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm> [<http://perma.cc/PU4R-YA66>].

175. THOMAS, *supra* note 164, at 369.

176. *Id.* at 370–71; see also 21 U.S.C. § 355a (2004).

177. Leslie Kushner, Note, *Incentivizing Postmarketing Pharmaceutical Product Safety Testing with Extension of Exclusivity Periods*, 19 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 519, 546 (2009).

178. See THOMAS, *supra* note 164, at 370–71.

179. Pamela Politis, *Transition from the Carrot to the Stick: The Evolution of Pharmaceutical Regulations Concerning Pediatric Drug Testing*, 12 WIDENER L. REV. 271, 282 (2005).

180. See 21 U.S.C. § 355a(b)(1).

181. For more information on the pros and cons of patent extension as an incentive for drug development behavior see Hathaway, *supra* note 25, at 171.

patent extension has the advantage of incentivizing desired pharmaceutical company behavior but it does not address any risk adverse-ness in the women needed to sign up for clinical trials.¹⁸² Thus, a patent extension may need to be paired with some “carrot” for individual women signing up for these potentially risky procedures.

B. Prescription Drug User Fee Act Filings

Pharmaceutical companies are required to file applications to the FDA accompanied by fees.¹⁸³ One possible incentive—to induce pharmaceutical companies to include more women in all stages of the drug development process—is to reduce the required filing fees, or to “jump” a drug to the front of the development line, thus allowing them to expediently recoup their investment by achieving faster FDA approval and market penetration.

The Prescription Drug User Fee Act (PDUFA)¹⁸⁴ “authorizes [the] FDA to collect fees from companies that produce certain human drug and biological products.”¹⁸⁵ PDUFA establishes three tiers of fees: application fees, establishment fees, and product fees.¹⁸⁶ PDUFA was established against the 1990s backlog in the drug approval process, which delayed the launch of many drugs to the market.¹⁸⁷ The backlog led to “drug lag,” where drugs were being approved by foreign health agencies before they were approved for United States patients.¹⁸⁸ PDUFA was enacted to make the drug approval process more effective and timely, increase the FDA budget with income from user fees, and hold the FDA accountable for meeting performance objectives in the drug approval time line.¹⁸⁹

182. *See id.* at 172.

183. *Frequently Asked Questions on Prescription Drug User Fees (PDUFA)*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm> [<http://perma.cc/DUH2-86X7>].

184. *Id.*

185. *Id.*

186. Under PDUFA, a 505(b)(1) application contains a full report of safety and effectiveness. A 505(b)(2) application is one where the investigations were conducted by another party. A supplement may also be submitted to “request to the Secretary to approve a change in a human drug application which has been approved.” *Id.* Application fees are one-time fees for New Drug Applications (NDA) and Biologics License Application (BLA). Establishment fees are an annual fee for manufacturers. Product fees are an annual fee for products on the market. *PDUFA and MDUFA History*, CAL. HEALTHCARE INST., http://www.chi.org/uploadedFiles/Legislative_Action/Federal_Issues/PDUFA-MDUFA-History.pdf [<http://perma.cc/NCX6-KXF2>].

187. *PDUFA and MDUFA History*, *supra* note 186.

188. *Id.*

189. *Id.*

Together, the three types of fees—application, establishment, and product—provide one-third of total FDA fee revenues for a fiscal year.¹⁹⁰ The total amount of PDUFA revenue that the FDA collects in user fees is “independent of the number of waivers or reductions in fees that are granted.”¹⁹¹

Target revenues are established in accordance with a statutory formula, and the amount of each type of fee (application, product, and establishment) is determined based on historical data of how many applications, products, and establishments were assessed fees in the previous fiscal year. Therefore, the more waivers or reductions are granted, the more fees must be increased the following year for applications, products, and establishments subject to fees to meet the annual statutory revenue targets.¹⁹²

Because of the structure of PDUFA fees, a solution whereby individual pharmaceutical companies are granted fee exceptions or have their products “jumped” to the front of the line may be unworkable. PDUFA fees fund the FDA to have a sufficient number of medical reviewers to process new drug applications.¹⁹³ Since the entire purpose of PDUFA was to expedite safe, new drug patents, decreasing the capacity of the FDA—by underfunding the system—to review drugs may be counterproductive.

CONCLUSION

It goes without saying that modern medicine has revolutionized the course of a human life in the 21st century. However, a course correction is needed when half of the population is left by the wayside to cope with medicine that has not been analyzed for sex-related response differences. Although great strides have been made since the days of thalidomide, gender differentials need to be accounted for—from cell line through Phase III clinical trials—for women to have parity in diagnosis, treatment, and efficacy.

To solve this problem, it is important to take into account the risk preferences of the women needed to enroll in potentially risky early drug trials. Previously suggested litigation-based solutions lack

190. *Id.*

191. *Guidance for Industry User Fee Waivers, Reductions, and Refunds for Drug and Biological Products*, FOOD & DRUG ADMIN. 2 (Sept. 2011), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079298.pdf> [http://perma.cc/WJ56-862W].

192. *Id.*

193. *PDUFA and MDUFA History*, *supra* note 186.

standing in current law. However, incentivizing pharmaceutical companies to put their not-inconsiderable resources into changing the risk preferences of women with marketing efforts and cash payouts is a way to leverage their power and size to the government's advantage.

A *qui tam* statute empowering specialized organizations, and closely monitored by the FDA to avoid settlement problems, could be the "stick" to encourage pharmaceutical companies to fulfill FDA-mandated guidelines for gender equality in development. A patent extension on new molecular entities that fulfill those same guidelines could be the "carrot" creating monetary incentives and reserves for the pharmaceutical companies. That money could cover marketing and cash payouts to encourage women to enroll. This two-pronged solution would both incentivize pharmaceutical companies and take into account the risk preference of the women needed to enroll. Laws that work to play on the incentives of all the parties involved have the best chance at harnessing the power of the pharmaceutical market to achieve gender parity in drug development.

SHANA F. OPPENHEIM*

* J.D. Candidate, William & Mary Law School, May 2016. B.A., New York University, 2011. The author would like to thank Professors Nathan Oman and Rebecca Green for their feedback throughout the writing process. The author would also like to thank Nancy Santanello for her invaluable comments. Additionally, the author would like to thank Barry Oppenheim, Erica Beacom, Lindy Gunderson, Caroline Caldwell, Kendall Kemelek, Georgia MacLean, and Tess Rowley for all of their support and counsel.