7 HOUS. J. HEALTH L. & POL'Y 127–150 R

ISSN 1534-7907

WOMEN AND THE FDA: REMEDYING THE PAST AND PRESERVING THE FUTURE

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I. INTRODUCTION

Men and women are different. Men and women react differently to the same disease, experience different symptoms, respond

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differently to medications,[1] and are often given different medical treatment.[2] We know that sex is an important factor in predicting responses to treatment, and we know that recognizing risks unique to women will help physicians select appropriate medical treatment.[3] Thus, it is very important to understand sex[4] differences in diseases, treatment, and effectiveness of medications.[5] This paper will examine the harm done to women with the focus on the stereotypical "70 Kilogram Man" in drug research, medical diagnosis, and treatment.[6] While intentional biases toward women have been addressed under current drug regulations promulgated by the Food & Drug Administration (FDA), the regulations still fail to utilize such information to the benefit of women.[7] Furthermore, with the health community still prescribing drugs that were approved in the past when women were not adequately represented in clinical trials, women are not guaranteed that the drugs they take are safe and effective.[8] By revisiting research that was necessary for initial approvals of such drugs, false perceptions of the past will be clarified and women will obtain better health care.

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[1] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, Pub. No. GAO-01-754, at 7 (2001), *available at* http://www.gao.gov/new.items/d01754.pdf (discussing women's physiological differences that cause different reactions to different types of drugs such as pain killers, over-the-counter and prescription cough and cold medications, and weight loss products).

[2] Carol Jonann Bess, *Gender Bias in Health Care: A Life or Death Issue for Women with Coronary Heart Disease*, 5 HASTINGS WOMEN'S L.J. 41, 43 (1995).

[3] *Id.*

[4] It is important to distinguish between the terms "sex" and "gender." "Sex" refers to the biological differences between men and women and distinguishes the genetic and physiological characteristics of the two sexes. "Gender" refers to one's identity as a man or woman and how social and cultural influences shaped this view based on one's sex. *See* Vivian W. Pinn, *Sex and Gender Factors in Medical Studies*: *Implications for Health and Clinical Practice*, 289 JAMA 397, 397 (2003).

[5] While the focus of this paper examines the problems the drug approval system causes for women, it is important to note that many of these concerns can be equally applied to other groups such as racial minorities, the elderly, and children. Although beyond the scope of this paper, these other groups are equally as important and should be addressed as well. *See generally* Jerry Gurwitz et al., *The Exclusion of the Elderly and Women From Clinical Trials in Acute Myocardial Infarction*, 268 JAMA 1417 (1992); Barbara A. Noah, *Racial Disparities in the Delivery of Health Care*, 35 SAN DIEGO L. REV. 135 (1998); Michelle Oberman & Joel Frader, *Dying Children and Medical Research: Access to Clinical Trials as Benefit and Burden*, 29 AM. J.L. & MED. 301 (2003).

[6] Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 HOUS. L. REV. 1201, 1209 (1996).

[7] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 4–5.

[8] *Id.* at 13.

Part I of this paper summarizes the historical battles women have fought in the drug approval process. This analysis recognizes the progress women have made by examining the initial FDA regulations and how they evolved into the FDA regulations in effect today. It also recognizes the problems that the regulations and FDA's management structure have still failed to solve. By looking at the problems in the current drug approval process, it is clear that the FDA is a passive agency that fails to properly require drug companies to follow its regulations. It is also clear that the present regulations do not adequately provide health care information relevant to both sexes. Without requiring analysis of the data sought by the regulations, the FDA and drug companies continue to ignore relevant information.[9] Part I also examines legislation currently under consideration in Congress and how it too fails to require the analysis of the data obtained. This information is vital in recognizing and understanding sex differences and to providing better health care for women.

Part II examines the problems caused by past practices when women were excluded or not adequately represented in clinical trials. These past trials that discriminated against women caused the stereotypical male to be treated as the "norm" in drug research, despite the fact that men and women are different.[10] Part II also examines the history of heart disease, in particular, noting how misconceptions about this disease have prevented women from receiving adequate health care.

Part III proposes that the FDA require such research to be revisited to ensure that older drugs are safe and effective in women. This information will help resolve some of the discrepancies of the past and will reveal any false perceptions of the present. By revisiting past research, drug makers were able to create new drugs to better treat African Americans. This has not only provided African Americans with better health care, but has also led to profits for the drug company. Similar research could also benefit women. Part III also explores solutions to remedy the inadequate drugs and treatment women currently receive by identifying the need for the FDA to implement regulations requiring the effectiveness of the drug to be documented and analyzed through post-marketing surveillance procedures. Acknowledging the lack of force in current post-mar-

[9] *Id.* at 4–5.

[10] Pinn, *Sex and Gender Factors in Medical Studies*: *Implications for Health and Clinical Practice supra* note 4, at 397.

keting surveillance regulations, Part III suggests that more action be taken to adequately ensure safe and effective drugs by threatening withdrawal of the drug from the market if this information is not sought or analyzed.

In conclusion, men and women are different. This concept has long been recognized by society. The FDA acknowledges this by requiring drug data be categorized by sex. However, the FDA needs to go one step forward by requiring this data to be analyzed in the drug approval process, and one step back by requiring the data to be revisited if the initial information was biased and potentially inapplicable to women.

II. A LOOK AT THE PAST, PRESENT, AND FUTURE

A. Past Problems: An Historical Overview of the FDA Regulations & the Problems They Caused Women

The FDA is responsible for ensuring that only safe and effective drugs reach the United States market.[11] In order to do this, the FDA has direct oversight over drug manufacturers throughout the entire drug approval process by granting approval of clinical trials, monitoring the results of the clinical trials, and making the ultimate decisions on drug approval.[12] After a drug has gone through preclinical research and testing, the drug manufacturer must submit an investigational new drug (IND) application to the FDA containing the results of prior tests and proposing a plan to assure safety to human participants during the necessary clinical trials for drug approval, thus ultimately persuading the FDA that the drug's effectiveness in humans will lead to commercial development.[13]

If the FDA approves the initial IND application, the drug manufacturer proceeds promptly with the three main phases of human clinical trials.[14] Phase I examines the safety, pharmacology, and metabolism of the drug in a relatively small group of healthy volunteers to determine any potential harm caused by the drug.[15] Phase II of clinical trials further confirms the safety of the drug and also determines the efficacy of the drug in a limited number of human par-

[11] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 5.

[12] *Id.*

[13] *Id.* at 6.

[14] *Id.*

[15] *Id.*

ticipants who suffer from an illness the drug was designed to treat.[16] Phase III studies thousands of patients over many months or years to determine the safety and efficacy of the drug on a larger scale and identifies any side effects that may arise.[17] During the time period of these trials, the drug manufacturers are required to submit annual reports to the FDA to update the agency on the progress of the clinical trials.[18] After all testing is over, to obtain FDA approval, the drug manufacturer must submit a New Drug Application (NDA) to the agency that includes the results of the studies, and specifically addressing drug safety and efficacy.[19] The information in the NDA enables the FDA to decide whether the drug's benefits outweigh its risks, thereby allowing the agency to ultimately approve the drug.[20]

Historically, women were excluded from clinical trials for drugs seeking FDA approval and from more general research studies due to well-intentioned but ultimately imprudent efforts at safeguarding women.[21] After two incidents occurred during clinical trials that caused harm to women and their unborn children, the FDA felt that excluding women from clinical trials would protect them from potential harm to both their reproductive capacities and to the lives of their fetuses.[22] In fact, a 1977 FDA guideline specifically excluded women of childbearing age from participating in drug research.[23] The guidelines broadly defined "women of childbearing potential" as all women capable of reproduction, resulting in widespread exclusion of women from clinical trials, in-

[16] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 6.

[17] *Id.*

[18] *Id*.

[19] *Id.*

[20] *Id.* at 5.

[21] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: FDA NEEDS TO ENSURE MORE STUDY OF GENDER DIFFERENCES IN PRESCRIPTION DRUG TESTING, Pub. No. GAO-HRD-93-17, at 2 (1992), *available at* http://archive.gao.gov/d35t11/147861.pdf.

[22] After the use of the sedative thalidomide, a drug taken to prevent miscarriages, caused 10,000 birth defects in other countries between 1959 and 1962, the FDA denied drug approval in the United States. Later, when it became evident in the 1970s that synthetic estrogen diethylstilbestrol (DES), a drug taken to protect against miscarriages, increased the risk of vaginal cancer and produced daughters with reproductive abnormalities, the public pressured the FDA to protect women and fetuses. *See generally* Jillian Hemstock, *Women in Clinical Trials—Where Are They?* 12 BUFF. WOMEN'S L.J. 25, 25–26 (2004) (providing an overview of the historical basis for the FDA guideline requesting the exclusion of women of childbearing age).

[23] FDA, U.S. DEP'T OF HEALTH, EDUC., & WELFARE, GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS, at 7 (1977) [hereinafter 1977 GUIDELINES].

cluding all pre-menopausal women on contraceptives or celibate women.[24] Even though the guidelines provided an exception for drugs treating life-saving diseases, women of childbearing potential were still not adequately included in clinical trials of these types partly because of the extra burdens these studies required for women participants.[25] Further, drug companies' fears of liability and safety concerns added to the exclusion of women of childbearing potential, and thus, most research studies focused primarily on middle-aged men.[26]

By the mid-1980s, however, the research community began to recognize that the lack of women in research studies had caused a detrimental effect on women's health.[27] Researchers concluded that women needed to be included in medical research studies because of sex-based differences in pharmacokinetics[28] and pharmacodynamics,[29] and the impact these differences had on drug safety and efficacy.[30] In short, women were being treated with medications that had never even been tested on one woman subject,[31] and the validity of research data obtained solely from men and extrapolated for clinical use to women was questionable.[32] Soon, women's advocacy groups began to demand equal access to experimental therapies in

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[24] Hemstock, *supra* note 22, at 27; *see also* Vanessa Merton, *The Exclusion of Pregnant, Pregnable and Once-Pregnable People (a.k.a. Women) from Biomedical Research*, 3 TEX. J. WOMEN & L. 307, 330–32 (1994).

[25] 1977 GUIDELINES, *supra* note 23, at 7; *see also*, Merton, *supra* note 24, at 336–37 (Recognizing that the guidelines for women participating in studies on drugs treating life-saving diseases require women participants to undergo pregnancy tests and contraceptive advising. The guidelines also require follow–up analysis for potential excretion of the drug in the milk produced by a woman if she became pregnant during or recently after the trial).

[26] Susan Epstein, *Tort Reform to Ensure the Inclusion of Fertile Women in Early Phases of Commercial Drug Research*, 3 U. CHI. L. SCH. ROUNDTABLE 355, 359 (1996).

[27] Sarah K. Keitt, *Sex & Gender: The Politics, Policy and Practice of Medical Research*, 3 YALE J. HEALTH POL'Y L. & ETHICS 253, 253 (2003).

[28] Pharmacokinetics is "the time course of the drug's absorption, distribution, metabolism (biotransformation), and excretion." *See* EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH: DOES SEX MATTER? 118 (Theresa Wizemann & Mary-Lou Pardue, eds., 2001).

[29] Pharmacodynamics is "the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure; also, such effects on the actions of a particular drug or drugs." *Id.* at 242.

[30] *See* Jean Hamilton & Barbara Parry, *Sex-related Differences in Clinical Drug Response: Implications for Women's Health*, 38 J. AM. MED. WOMEN'S ASS'N 126, 130 (1983).

[31] Lisa A. Eckenwiler, *Pursuing Reform in Clinical Research: Lessons from Women's Experience*, 27 J.L. MED. & ETHICS 158, 159 (1999).

[32] *See* Bess, *supra* note 2, at 49 (stating that "the problem with this male model is that information is extrapolated to women with effects ranging from incorrect to lethal," and that

early clinical phases.[33] In response to all of these concerns, the Task Force for the United States Public Health Service concluded in 1985 "that the lack of a research focus on women's health issues compromised the quality of health information available to women as well as the health care they received."[34]

In recognition of the enormous sex disparities in clinical research, in 1988, the FDA revised its guidelines by requesting evaluation of sex-related differences of the tested drug.[35] However, less than half the studies submitted that year included such data.[36] Furthermore, the General Accounting Office (GAO) issued a report in October of 1992 based on a survey conducted from 1988 to 1991 of drug manufacturers to determine the number of women participants in clinical trials.[37] The report found that in a quarter of the surveyed responses, the drug manufacturers stated that they did not "deliberately recruit representative numbers of women as participants in drug trials."[38] Furthermore, over half the surveyed responses confirmed that the FDA had requested women to be included in clinical trials, but the remainder stated the agency had not.[39] The report concluded that in over sixty percent of the drugs approved, the clinical trials did not include women participants proportionate to the number of women in the population with the disease.[40] Moreover, the report stated that even in 1992, the FDA's review of NDAs concluded that manufacturers were still not including analysis of safety and effectiveness by gender.[41]

In 1993, the FDA lifted its blanket exclusion on women of childbearing age and "recommended" the inclusion of women in

"examples abound that extrapolation to women of a drug's effects on male research subjects is inaccurate and potentially dangerous").

[33] *See* Rothenberg, *supra* note 6, at 1239.

[34] Keitt, *supra* note 27, at 256.

[35] CTR. FOR DRUG EVALUATION & RESEARCH, GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS, at 31–40 (1988), *available at* http://www.fda.gov/cder/guidance/statnda.pdf.

[36] Ruth B. Merkatz et al., *Women in Clinical Trials of New Drugs—A Change in Food and Drug Administration Policy*, 329 NEW ENG. J. MED. 292, 296 (1993).

[37] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: FDA NEEDS TO ENSURE MORE STUDY OF GENDER DIFFERENCES IN PRESCRIPTION DRUG TESTING, *supra* note 21, at 2.

[38] *Id.*

[39] *Id.*

[40] *Id.* at 2–3.

[41] *Id.* at 12.

medical research.[42] However, drug companies dismissed this recommendation because they believed that women's hormonal fluctuations, body size, and physiological composition would cause methodological problems, rendering the studies ineffective.[43] Researchers believed that "valid interpretation require[d] that subjects be as homogenous as possible" and that women's hormonal variations could cause problems in the study, thus rationalizing the exclusion of women from the clinical trials.[44] More importantly, the recommendations may have been dismissed by drug companies because they did not have the force of law.[45]

That same year, Congress passed the National Institutes of Health Revitalization Act, requiring the Director of the National Institutes of Health (NIH) to ensure that women are included in clinical trials.[46] The Act stated that women needed to be included in clinical research studies and in Phase III of clinical trials, and it noted that cost would not be a valid reason to exclude women.[47] This Act did provide exceptions for drug companies to exclude women in clinical research, such as if it was inappropriate to include women out of respect for their health, for the purpose of the research, or, as a catch-all, as the NIH Director "may designate."[48] The Act also provided an exception if prior studies supported the concept that there were no significant sex differences between subgroups using the drug.[49] Given these exceptions, drug companies were only "required" to include women if previous clinical trials supported the existence of significant sex-based differences.[50] However, at this time, data on sex-based differences was not typically compiled, nor analyzed.[51] In turn, this did not effectively require drug companies to include women in clinical trials. Later that year, the FDA issued guidance recommending that clinical trials include women in NDAs in numbers sufficient to detect clinically sufficient

[42] *See* Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, 58 Fed. Reg. 39,113, 39,408–09 (proposed July 22, 1993).

[43] Eckenwiler, *supra* note 31, at 159.

[44] *Id.*

[45] Rothenberg, *supra* note 6, at 1241.

[46] National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103–43, 107 Stat. 122 (codified as amended in scattered sections of 42 U.S.C.).

[47] *Id.*

[48] *Id.*

[49] *Id.*

[50] *Id.*

[51] Rothenberg, *supra* note 6, at 1239–41.

gender differences in drug response.[52] However, once again, this recommendation was ignored because it did not carry the force of law.[53]

In 1997, Congress passed the FDA Modernization Act, which included a provision requesting that the "Secretary [of Health and Human Services], in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials."[54] Thereafter, in 1998, the FDA amended its regulations governing NDAs to require sponsors to break down the drug safety and effectiveness data by gender, age, and race, and to give the FDA the power to refuse any application without an adequate breakdown of drug safety and effectiveness.[55] The revised regulations also required that IND applicants tabulate, in their annual reports, the number of different subgroups, including women, who were enrolled in clinical studies.[56] In 2000, the FDA Final Rule on INDs empowered the agency with the right to refuse any application excluding women from drug trials for drugs intended to treat life-threatening diseases where women were excluded only because of a risk or a potential risk of reproductive or developmental toxicity from the tested drug.[57]

B. Present Problems: The Problems Women Face Today Under Current FDA Regulations

All of these revised recommendations and regulations recognize the significance of including women in clinical trials, and they demonstrate that there has been progress in recognizing a means of curing sex-based disparities in clinical research. However, they have failed to solve the problem in its entirety. Two issues, in particular, remain with the current FDA regulations. First, the agency has been too passive, and there is no incentive for drug companies to document the requested data because the FDA does not incorporate the

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[52] *See* Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, *supra* note 42, at 407.

[53] Rothenberg, *supra* note 6, 1239–41.

[54] Pub. L. No. 105–115, 111 Stat. 2296 (codified at 21 U.S.C. § 355(b)(1) (1994)).

[55] 21 C.F.R. § 314.50(d)(5)(v)–(vi) (1998).

[56] 21 C.F.R. § 312.33(a) (1998).

[57] 21 C.F.R. § 312.42 (2000).

regulations into practice.[58] In fact, a GAO report in 2001 found that one-third of approved NDAs failed to meet the 1998 requirement to break down the safety and efficacy data by sex.[59] The GAO's investigation also revealed that thirty-nine percent of IND applicants did not include the required demographic information in their annual reports,[60] yet no action was taken by the agency. GAO concluded that:

> FDA has not effectively overseen the presentation and analysis of data related to sex differences in drug development. There is no management system in place to record and track the inclusion of women in clinical drug trials or to monitor compliance with relevant regulations, so FDA is unaware that many new drug application submissions failed to meet standards.[61]

This is evident in the fact that while the regulations provide the FDA with explicit authority to refuse NDAs without adequate data,[62] no such applications were denied at the time of the report even though one-third of them failed to include the necessary data.[63] The report ended with a recommendation that the FDA adopt management strategies to ensure compliance with current regulations, and that NDA reviewers address sex-based differences identified from the data in the applications.[64]

Second, the regulations do not require that the data be analyzed by sex or other various subgroups.[65] The 1998 regulations are so vague that they undermine the proposition that information recognizing sex-based differences is vital to women's health.[66] Instead of mandating the study of the information requested by FDA, the

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[58] *See* Hemstock, *supra* note 22, at 28–31.

[59] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 3.

[60] *Id.*

[61] *Id.* at 4.

[62] *Id.* at 11.

[63] *Id.* at 3.

[64] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 20.

[65] *See generally* 21 C.F.R. § 314.50 (1998) and 21 C.F.R. § 312.42 (2000).

[66] The GAO report issued in 2001 expressed concern with the new regulations because they were less specific than the 1993 guidelines. The 1998 regulations did carry the force of law, but neglected to incorporate many of the 1993 recommendations, including the need to analyze clinical data by sex and to evaluate differences in phamacokinectics when necessary. The 1998 regulations only require the "presentation" of such data, which merely requires the data be included in the NDA and categorized by sex, but it does not appropriately require the analysis of the information obtained. *See* U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 11–12.

regulations merely require companies to categorize safety and efficacy data categorized by sex.[67] Without analysis of this data, however, differences in pharmacokinetics cannot be evaluated.[68]

This failure has had a clear impact on women's health. In fact, the GAO found that out of the ten prescription drugs removed from the market from 1997-2000, nine of the drugs posed a greater degree of harm to women compared to men.[69] Four of the drugs were prescribed equally to both sexes, but caused women more harm than men; four others caused women more harm, and were prescribed to more women initially; and one drug was recognized as a type of drug resulting in negative effects for women.[70] If this information had been analyzed during clinical trials and explained in the NDA, the FDA could have prevented the harm these drugs later caused to women by initially denying approval.[71] This demonstrates the importance of requiring the analysis of data obtained from clinical trials, rather than simply entering the information on a form. With this knowledge, the FDA will have the power to ensure that women receive safe and effective drugs and to prevent harm from drugs negatively affecting women's health.

Treatment of sex disparities in clinical research has significantly improved, but many issues are still unresolved.[72] Women are now included in clinical trials, yet the data obtained from the trials are still not adequately utilized.[73] Analysis of this data is critical to understanding the differences in responses to drugs between the sexes.[74] While new legislation has been introduced in Congress to try to resolve this issue, it also fails to require the data be appropriately analyzed.[75] The proposed legislation would amend the Public Health Services Act to require NDAs and IND applications to in-

[67] *See generally* 21 C.F.R. § 314.50 (1998); 21 C.F.R. § 312.42 (2000).

[68] Bess, *supra* note 2, at 49–50.

[69] U.S. GEN. ACCT. OFF., DRUG SAFETY: MOST DRUGS WITHDRAWN IN RECENT YEARS HAD GREATER HEALTH RISKS FOR WOMEN, Pub. No. GAO-01-286R, at 3 (2001), *available at* http://www.gao.gov/new.items/d01286r.pdf (the drugs removed from the market that posed a greater degree of harm to women included: the appetite suppressants Pondimin and Redux; antihistamines Seldane and Hismanal; Posicor, a cardiovascular drug; Rezulin, a diabetes drug; and Propulsid and Lotronex, both gastrointestinal drugs).

[70] *Id.* at 2.

[71] *See id.* at 2–5.

[72] *See generally* U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1.

[73] *Id.* at 13.

[74] Hemstock, *supra* note 22, at 31.

[75] Heart for Women Act, S. 2278, 109th Cong. § 2 (2006).

clude "information stratified by gender, race and ethnicity, including any differences in safety and effectiveness."[76] The legislation further requires this stratified information be made available to the public in a timely manner if the drug is approved.[77] In addition, individuals reviewing these applications must ensure that such information is included.[78] The legislation reiterates the importance of obtaining such data, but neglects to require the data be analyzed for the various listed subgroups.[79] Both Congress and the FDA recognize the importance of collecting data on sex-based differences in drug safety and efficacy, but they fail to properly utilize this data by requiring implement regulations to require further analysis.[80] In short, both the current FDA regulations and the legislation under consideration by Congress should be amended to mandate analysis of sex-based data in all drug applications.

III. RECOGNIZING PAST MISCONCEPTIONS

A. Sex Matters: Medical Differences Between Men and Women

Although current regulations are not perfect, they represent progress that can bring both men and women more effective treatment and medication in the future. However, many sex disparities and past misperceptions remain unchallenged.[81] We know that sex matters.[82] The Institute of Medicine has reported that "[a]n additional and more general reason for studying differences between the sexes is that these differences, like other forms of biological variation, can offer important insights into underlying biological mechanisms."[83] The report further explains the importance of studying differences in sex because of the "multiple, ubiquitous differences in

[76] § 3(a)(5)(A).

[77] § 3(A)(5)(D).

[78] § 3(a)(5)(C).

[79] *See* Heart for Women Act, S. 2278, 109th Cong. § 2 (2006) (mandating collection but not analysis of stratified gender information).

[80] *See id. See generally* U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 7.

[81] *See* Pinn, *Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice*, *supra* note 4 (discussing historical gender bias and areas of research where improvements have been made).

[82] *See* U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 7 (noting that evidence exists that drugs are not always equally effective for both sexes).

[83] Pinn, *Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice*, *supra* note 4, at 397–98 (quoting Wizemann, *supra* note 28, at 4).

the basic cellular biochemistries of males and females that can affect an individual's health . . . are a direct result of genetic differences between the two sexes."[84] The American Medical Association has also expressed concern that "medical treatment for women are based on a male model, no matter that some diseases manifest themselves differently in each gender, or that women and men may react differently to treatments."[85] One example, of sex-based differences is that men and women metabolize drugs at different rates.[86] One study comparing the way men and women metabolize drugs with the way men and women metabolize alcohol found that women's body size and muscle mass allow women to metabolize alcohol at different rates than men, which in turn produces different responses to alcohol.[87] These reasons, along with differences in hormones and in liver functioning, are thought to be part of the reason why men and women respond differently to drugs.[88]

Differences are further demonstrated by a study that found women wake up almost twice as fast as men from anesthesia.[89] There are also known differences between men and women in pain tolerance and the way in which each sex responds to various pain medications.[90] For example, kappa opiods, a form of morphine-like painkillers, offers long-lasting relief for women, but can actually make pain worse for men at certain dosages.[91]

There are also differences in how diseases present between the sexes.[92] For example, women with heart disease do not typically experience the "elephant standing on [the] chest" type of pain that men experience, and instead, often express more subtle symptoms.[93] All of these differences are known because researchers have studied them.[94] The perception that the "70 Kilogram Man" is the norm has

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[84] Wizemann, *supra* note 28, at 4.

[85] Susan Dennehy, *Understanding Heart Disease in Female Patients*, 39 TRIAL 36, 38 (2003).

[86] Hemstock, *supra* note 22, at 27.

[87] *Id.*

[88] *Id.*

[89] Judith Levine Willis, *Equality in Clinical Trials: Drugs and Gender*, FDA CONSUMER SPECIAL REP., at 1 (1997), *available at* http://www.fda.gov/oashi/aids/equal.html.

[90] *Id.*

[91] *Id.*

[92] Dennehy, *Understanding Heart Disease in Female Patients, supra* note 85, at 38; *see also* Council on Ethical and Judicial Affairs, Am. Med. Ass'n, *Gender Disparities in Clinical Decision Making*, 266 JAMA 559–62 (1991).

[93] *Id.* at 38.

[94] *Id.* at 36–38.

long been questioned and proven false.[95] And yet little has been done to verify the accuracy and efficacy of drugs approved when women were excluded from or inadequately represented in clinical trials. Would revisiting this research to effectively analyze sex differences produce better health outcomes for men and women? If there is such a strong concern for analyzing future information by sex, should there not be a similar concern that previously approved drugs be analyzed this way as well? Certainly, areas of medical research with known sex-based differences should be reanalyzed to better treat both men and women.

B. Heart Disease: Perceptions of the Past Creating Problems for Today

One area that has received much debate because of the medical differences between men and women is heart disease.[96] For example, research has proven that men and women respond differently to the actual disease.[97] Men and women often exhibit different symptoms, and different treatments may be required.[98] Similarly, the effectiveness of medications used to treat heart disease differs between men and women.[99] For example, an early study on heart disease conducted on 22,000 male subjects tested the benefits of aspirin in the men's daily diet.[100] The study concluded that a daily regime of aspirin would prevent heart attacks for all adults.[101] Although the study did not include any women subjects, the study results were extrapolated to women.[102] At that time, there appeared to be no problem with applying this study to both sexes because heart disease was thought to be a man's disease, and so the main concern of the study was men's health.[103] Only later, after studies revealed that heart disease was also the number one killer for women, was this approach questioned.[104]

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[95] Rothenberg, *supra* note 6, at 1209.

[96] *See generally*, Dennehy *Understanding Heart Disease in Female Patients, supra* note 85, at 36.

[97] Rothenberg, *supra* note 6, at 1210.

[98] Dennehy, *Understanding Heart Disease in Female Patients*, *supra* note 85, at 37–38.

[99] *See* U.S. GEN. ACCT. OFF., DRUG SAFETY: MOST DRUGS WITHDRAWN IN RECENT YEARS HAD GREATER HEALTH RISKS FOR WOMEN, *supra* note 69, at 5.

[100] Rothenberg, *supra* note 6, at 1210.

[101] *Id.*

[102] *Id.*

[103] Bess, *supra* note 2, at 51.

[104] Hemstock, *supra* note 22, at 25.

Thereafter, a study was conducted by the Women's Health Institute solely on women to see if the results of the earlier aspirin study would be validated.[105] They were not.[106] In fact, the study reported very different outcomes in women than the previous study had yielded in men.[107] Major cardiovascular events, including myocardial infarction among women younger than 65 years old were not affected by a low dose of aspirin.[108] Only women 65 years of age or older did aspirin reduce the risk of myocardial infarctions.[109] And yet statistics show that women under the age of 65 are more than twice as likely to die from a heart attack as men in this same age category.[110] This is a prime example of how the standard male model for drug studies has lead to misconceptions in the treatment of women. It illustrates that sex-based differences in medical care may exist due to past discrimination in clinical trials. If women had been included in the initial aspirin study, it would have been clear that the drug was not as effective in women in preventing cardiovascular problems.

Similarly, the 2001 GAO study found that four of the ten drugs recently withdrawn from the market increased the risks of fatal cardiac arrhythmias in women.[111] Why is this? Many believe that the past discrimination in clinical trials has added to the lack of information on women's health in heart disease.[112] It is now recognized that women react differently to heart disease and to the medications used to treat heart disease, in part, because the distance between the heart muscle's contractions is biologically longer in women.[113] Certain medications treating heart disease further extend the distance between the heart muscle's contractions, an effect that increases the risk of cardiac arrhythmias in women taking these drugs.[114] Furthermore, male hormones help restrain the heart's sensitivity to the

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[105] Vivian Pinn, *Research on Women's Health: Progress and Opportunities*, 294 JAMA 1407, 1409 (2005).

[106] *Id.*

[107] *Id.*

[108] *Id.*

[109] *Id.*

[110] Susan A. Dennehy, *Are We Missing the Big One? Heart Disease in Women: The Number One Killer*, 1 ATLA ANN. CONVENTION—WOMEN'S TRIAL CAUCUS 1297, at 2 (2004).

[111] *See* GEN. ACCT. OFF., DRUG SAFETY: MOST DRUGS WITHDRAWN IN RECENT YEARS HAD GREATER HEALTH RISKS FOR WOMEN, *supra* note 69, at 4.

[112] Pinn, *Research on Women's Health: Progress and Opportunities*, *supra* note 105, at 1407.

[113] *Id.*

[114] *Id.*

drugs given to treat heart disease.[115] These differences are now recognized in the treatment of heart disease, and help physicians provide more appropriate health care to women.

Moreover, women often evidence different symptoms of heart disease.[116] Women often experience "neck and shoulder pain, nausea, vomiting, fatigue or shortness of breath."[117] In the past, these symptoms were dismissed by medical care providers because they were not the typical crushing chest pain that men normally experience from cardiovascular disease.[118] These male symptoms were the "norm" and affected the way women dealt with their symptoms and the way medical providers treated them.[119] For a long time, many women were turned away from medical facilities and their symptoms were dismissed as gastrointestinal or emotional in nature.[120] Without the various studies conducted on women with heart disease, this information would not have been known and women's health would be at greater risk for inadequate care and treatment. In fact, since many of the initial clinical trials on heart disease did not provide information adequate to treat women with heart disease, more than fourteen clinical trials in the past ten years have been conducted to define the differences in women and to help prevent and treat cardiovascular disease in ways unique to women.[121]

IV. A PROPOSAL: REVISITING RESEARCH TO GENERATE SAFE AND EFFECTIVE DRUGS FOR WOMEN

A. FDA's Obligation to Ensure that Safe and Effective Drugs Reach the U.S. Market

Heart disease was initially considered a man's disease even though it has been the number one killer of women since the 1900s and has killed more women than men since 1984.[122] Women were

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[115] *Id.*

[116] Pinn, *Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice*, *supra* note 4, at 398.

[117] Dennehy, *Are We Missing the Big One? Heart Disease in Women: The Number One Killer*, *supra* note 110, at 3.

[118] *Id.* at 2–3.

[119] *Id.* (stating that women are more likely to be discharged from the hospital because the practice of making a diagnosis is based on a male model).

[120] *Id*.

[121] Pinn, *Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice*, *supra* note 4, at 398.

[122] Emily Sohn, *Pictures of Health*, 39 MINN. MONTHLY 1, 2 (2005).

initially excluded from clinical trials to determine effects of new medications in preventing and reducing symptoms of heart disease.[123] Now, new studies have revealed many of the misperceptions that have been applied to women based on the male model.[124] With the knowledge gained from these new studies, we are able to recognize the symptoms typical to women and to treat their heart disease more effectively. But what has this experience taught us? Does it not suggest that there could be similar misconceptions about other diseases in need of new studies? Is there not an essential need to find this information, for the better treatment of both men and women? And where should we start?

Certainly, trials that entirely excluded women should be revisited to verify the accuracy of the results obtained. But what about trials that just underrepresented women? A 1992 GAO report found that for over sixty percent of the drugs approved from 1988 to 1991, the representation of women in the study was less than the representation of women in the population with the corresponding diseases.[125] This Article proposes that we go back and retest these drugs to confirm the results in women, to correct any relevant therapeutic misconceptions, and to better diagnose diseases. As one researcher has said, "these cardiovascular-drug findings typify the need for more research and a better understanding of the need for sex-based analyses of responses to drugs and other pharmacologic interventions, with closer clinical attention to detect sex-based adverse effects."[126] In another article, the same author stated that "results from studies that have previously been conducted only in men—such as a number of studies related to diagnosis and treatment of cardiovascular disease (CVD)—now should be validated in women."[127] Should this apply to any study that did not adequately include women as well? The answer is clearly yes.

The FDA's purpose is "to ensure that safe and effective food, drugs, medical devices, and cosmetics reach the United State's market."[128] Thus, the FDA's purpose is twofold. Not only is the agency

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[123] *See generally* Rothenberg, *supra* note 6, at 1209-10.

[124] *See* Pinn, *Research on Women's Health: Progress and Opportunities*, *supra* note 105, at 1409.

[125] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: FDA NEEDS TO ENSURE MORE STUDY OF GENDER DIFFERENCES IN PRESCRIPTION DRUG TESTING, *supra* note 21, at 2–3.

[126] Pinn, *Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice*, *supra* note 4, at 399.

[127] Pinn, *Research on Women's Health: Progress and Opportunities*, *supra* note 105, at 1407.

[128] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 5.

required to ensure that medicines are safe for both sexes, it must assure that they are effective as well. If revisiting research can assure better drug safety for women, then it should be done. It is known that women are prescribed more drugs than men and have more adverse effects from medications than men.[129] It is also known "over 100,000 people die in the United States each year from adverse reactions to medications, making them the fourth leading statistical cause of death in this country."[130] Retesting of drugs could help lower these statistics.

The FDA is also required to ensure that only effective drugs reach the U.S. market.[131] If the FDA merely ensures that a drug is effective in men, the agency is not meeting this mandate. If retesting of drugs is necessary to ensure drug effectiveness in women, the FDA should demand retesting. This research will not only identify differences in men and women, but will prevent harm to women due to past misperceptions and research exclusions, and will allow researchers to assess whether women actually benefit from drugs that were initially studied in men. This will allow women's symptoms not to be dismissed when based purely on a stereotypical male model, and in the end, will lead to better overall health care for women.

B. An Example: Research Revisited, Misperceptions Revealed, and a More Effective Drug Created

Not only will these studies identify discrepancies in past research, but information recognizing sex-based differences can allow drug companies to tailor new drugs to reduce those disparities. In fact, a growing number of drug companies are tailoring their research by race to better treat patients and eliminate health disparities.[132] For example, BiDil, a drug approved by the FDA in June 2005, is used to treat heart failure specifically in African Americans.[133] In the process of seeking FDA approval, Nitromed, Inc., the drug's manufacturer, stated that "death rates from heart failure are

[129] Bess, *supra* note 2, at 49.

[130] Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 449 (2000).

[131] U.S. GEN. ACCT. OFF., WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 1, at 5.

[132] *See generally* Sandra Soo-Jin Lee, *Racializing Drug Design: Implications of Pharmacogenomics for Health Disparities*, 95 AM. J. PUB. HEALTH 2133 (2005).

[133] *Id.* at 2136.

more than twice as high in black patients as in white patients."[134] This difference could be due to "a pathophysiology found primarily in black patients that may involve nitric oxide insufficiency."[135] The drug company later stated that "observed racial disparities in mortality and therapeutic response rates in black heart failure patients may be due in part to ethnic differences in the underlying pathophysiology of heart failure."[136] In fact, a study comparing the effectiveness of BiDil in African Americans compared to Caucasians found that the drug was more effective in African Americans.[137] BiDil is comprised of a combination of two drugs, hydralazine and isosorbide dinitrate (H/I).[138] Another drug used to treat heart failure is enalapril, an ACE inhibitor.[139] The study found that "the 'H-I' combination appears to be particularly effective in prolonging survival in black patients," while, "[i]n contrast, enalapril shows its more favorable effect on survival, particularly in the white population."[140] Thus, by analyzing the data by race, a more effective drug for African Americans was developed.

The benefits of this new information illustrate the need to revisit drugs and refine our knowledge of key differences in effectiveness of drugs when used in women compared to men. The studies performed on BiDil also show the need for drugs to be tailored to groups based on sex as well as race. Without the study revisiting the already approved drug enalapril and comparing it to a new drug seeking FDA approval, many African Americans would be without an effective treatment for heart disease.

Similarly, Nebivolol, a nitric-oxide-enhancing beta-blocker, is currently undergoing Phase III clinical trials and seeking FDA approval to treat hypertension in African Americans.[141] Typically, beta-blockers are not used for treating hypertension in African Americans because of a perception within the medical community that this form of medication is not effective for this group of pa-

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[134] Johnathan D. Kahn, *How a Drug Becomes "Ethnic": Law, Commerce, and the Production of Racial Categories in Medicine*, 4 YALE J. HEALTH POL'Y L. & ETHICS 1, 2 (2004).

[135] *Id.*

[136] *Id.*

[137] *Id.* at 17.

[138] *Id.* at 12.

[139] Kahn, *supra* note 134, at 12.

[140] *Id.*

[141] *Drug Could be Future Treatment for Hypertensive African Americans Hypertension*, HEART DISEASE WKLY., Aug. 14, 2005, at 130, *available at* 2005 WLNR 12287553.

tients.[142] However, studies of Nebivolol show that the drug actually works better in African Americans when compared to other groups.[143] One reason researchers believe Nebivolol is more effective in African Americans than other beta-blockers is the fact that it is a nitric-oxide enhancing drug, which compensates for the reduced production of nitric oxide in African American patients.[144] One researcher noted that this study ultimately undermines the perception that beta-blockers are not effective in African Americans.[145] This is another example where false perceptions have molded our view of appropriate medications, based on studies excluding many relevant subgroups. It reaffirms the belief that in continuing and revisiting research in areas with known disparities between populations, better health care can be provided for all.

C. Necessary Steps to Provide Safe and Effective Drugs to Women: Augmenting FDA's Power Post-Drug Approval

While it seems clear that some research needs to be revisited to determine the effectiveness of drugs in women, it is not clear how this can be done. This article proposes that the FDA implement post-marketing regulations requiring drug manufacturers to adhere to procedures that will ensure that only safe and effective drugs reach and remain on the U.S. market. Drug companies would not only be required to do so, but would have an incentive to adhere to these procedures because the retesting of drugs could yield economically viable results for drug companies if such information leads to drugs tailored to women.

When examining the need for the FDA to implement post-marketing procedures, it is important to recognize the pre-existing problems in the post-marketing drug surveillance system and in the lack of information sought by the regulations. The current post-marketing surveillance system provides the FDA the ability to monitor the safety and efficacy of new drugs in the U.S. market.[146] The system couples mandatory reports from drug manufacturers with vol-

[142] *Id.*

[143] *Id.*

[144] *Id.*

[145] *Id.*

[146] *See generally* 21 C.F.R. § 314.80 (1999). *See also* Noah, *Adverse Drug Reactions*, *supra* note 130, at 466–67 (providing an overview of the post-marketing surveillance system and the problems it encompasses).

untary reports from health care providers, combining them into a database that is then evaluated by FDA personnel.[147] This system has the potential to be as effective as its pre-drug approval controls, but has been continuously criticized due to the agency's failure to utilize its power post-marketing.[148] A recent GAO report stated that "FDA lacks a clear and effective process for making decisions about, providing management oversight of, post-market drug safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints."[149] The lack of communication among FDA personnel in reviewing the information received and the lack of agreement in reaching a decision on what action to take, leads to a delay in information released to the public and permits a potentially unsafe drug to remain on the market.[150] The GAO report provides a thorough analysis of the problems with the surveillance system and recommends to Congress to "consider expanding FDA's authority to require drug sponsors to conduct post-market studies, such as clinical trials or observational studies, as needed, to collect additional data on drug safety concerns."[151]

An additional problem exists in the data sought as part of the current post-marketing surveillance system. All the regulations currently require after a drug is approved is that the applicants report any adverse side effects to the FDA as soon as possible.[152] This system needs to be strengthened by implementing new regulations requiring research to be revisited when women were not adequately included in clinical trials and by requiring drug manufacturers to adhere to the post-marketing regulations. The FDA regulations should similarly require mandatory reporting when drug effectiveness varies between different groups. Currently, the FDA requires that drug manufacturers issue Annual Reports every year within sixty days of the approval date, including a summary of any significant new information that could affect the safety, effectiveness, or

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[147] *See generally* 21 C.F.R. § 314.80 (1999). *See also* Noah, *Adverse Drug Reactions, supra* note 130, at 466–67.

[148] U.S. GEN. ACCT. OFF., DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS, Pub. No. GAO-06-402, at 1 (2006), *available at* http://www.gao.gov/new.items/d06402.pdf.

[149] *Id.* at 5.

[150] *Id.*

[151] *Id.* at 36.

[152] *See* 21 C.F.R. § 314.80 (1999).

labeling of the product.[153] The FDA should require that this information include differences in safety and efficacy, categorized and analyzed by sex. Once this information is found, the drug company should be required to revisit the initial research to investigate these differences between the sexes. At a minimum, this information should be available to enable other researchers to further study the effectiveness of the drug among the different subgroups.[154] This will not only help regulate newly approved drugs with effectiveness that varies between sexes and among other various subgroups, but it will also address drugs that were approved in the past when inequalities in clinical trials existed. Since the controlled environment of clinical trials is not always an adequate reflection of the drug's use in the general population, this procedure can also be helpful in confirming the safety and efficacy of the drug within large patient populations.[155]

The FDA can further ensure that drug companies adhere to these recommended regulations by threatening to withdraw the drug from the market if the company fails to seek analysis of safety and efficacy data by sex or to reveal such data to the FDA. By implementing procedures similar to the regulations in place for initial drug approval, the FDA will assure the public that drugs currently marketed in the U.S. are safe and effective. When such research is being revisited, the FDA can require that drug companies reveal differences in effectiveness between sexes to the public and require these differences to be included on the label of the drug itself. With this knowledge, health care providers would be able to better choose drugs for individual patients.

This information should be actively sought by drug companies and must be reported to the FDA with analysis of safety and efficacy data by sex.[156] This information is vital to the entire community and is essential in carrying out the FDA's job. Currently, the FDA is not utilizing its post-marketing surveillance power to its utmost ability.[157] This is evidenced by the fact that the FDA receives an

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[153] *See* § 314.81 (1999).

[154] *See generally* Lee, *supra* note 132, at 9 (requesting that the FDA "require investigators and companies that attribute differential drug response to race to pursue additional research that further explicates the underlying mechanisms . . . [or make this research] available to enable other researchers to further study the basis for findings of difference among groups").

[155] Noah, *Adverse Drug Reactions*, *supra* note 130, at 459.

[156] *Id.* at 460; *see* Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, *supra* note 42, at 39,409.

[157] Noah, *Adverse Drug Reactions*, *supra* note 130, at 449–54.

estimated 230,000 reports of potential adverse drug reactions, ten percent of which raise concerns about serious reactions to the drug that were not revealed in the initial clinical trials, yet the agency only employs an estimated fifty-five full-time employees to review post-approval drugs.[158] In contrast, over 1,700 full-time employees engage in pre-market review of new drug applications.[159] By implementing regulations to require post-approval evaluation of drug efficacy, and to ensure adequate review by the FDA, the agency can implement a procedure to assure more effective drugs for the entire population.

Furthermore, retesting of drugs could yield economically viable results for drug companies if such information leads to drugs tailored to women. For example, BiDil was initially not a drug tailored to African Americans.[160] In fact, it was initially denied FDA approval as a drug to be used by the general public for congestive heart failure because it did not provide any improvement in overall treatment.[161] After the denial, the initial drug company backed out of the deal and the property rights reverted back to its patent holder, cardiologist Jay Cohn.[162] Not wanting BiDil to be deemed a failure, Cohn revisited the research conducted and discovered that African Americans benefited greatly from the drug.[163] In turn, Cohn later assigned the patent rights to NitroMed, which then initiated more studies solely on African Americans and ultimately won FDA approval of the drug specific to this population.[164] The drug has been very profitable for NitroMed, which went public in November of 2003, offering six million common shares priced at eleven dollars each with a market cap of $305 million.[165] Thus, identifying genetic differences by sex, race, and ethnicity, and then tailoring drugs to specific genetic groups, can lead to significant profits for drug companies.[166] As the Multicultural Pharmaceutical Marketing and PR conference stated in an announcement in 2004, "major U.S. drug manufacturers are making it a high priority area to cultivate relationships with ethnic consumers, physician groups, community net-

[158] *Id.* at 452.

[159] *Id.*

[160] Kahn, *supra* note 134, at 16.

[161] *Id.* at 15.

[162] *Id.* at 15–16.

[163] *Id.* at 16–18.

[164] *Id.* at 18.

[165] Kahn, *supra* note 134, at 26.

[166] *Id*. at 25.

works and other key stakeholder groups to uncover new market growth."[167] Certainly women should be considered another "key stakeholder group," considering they are the major consumers of health care and prescription drugs.[168] Statistics also show that women make the majority of health care decisions for the family.[169] So by winning over women in general, drug companies could be winning profits as well. Therefore, drug companies may be willing to revisit older research to provide more effective drugs for women.

V. CONCLUSION

Evidence proves that men and women are treated differently under the current FDA regulations. The FDA recognizes the significant evidence that men and women are biologically different, but the agency has failed to implement regulations to remedy this. Problems exist throughout the entire drug approval process and in the post-marketing surveillance procedures. A solution is needed to provide women the safest and most effective drugs, to identify ineffective drugs, and to clarify any misperceptions created. While it is important to recognize the improvement the FDA has made in including women in clinical trials, it is essential to understand that this is not enough. This paper proposes that the agency implement regulations requiring drug manufacturers to analyze safety and efficacy data by sex, and to revisit research conducted without adequate representation of women to assure its safety and efficacy. This proposal would provide the public with assurance that the FDA is doing its job by ensuring safe and effective drugs in the U.S. market for both men and women.

[167] *Id.*

[168] Pinn, *Sex and Gender Factors in Medical Studies*, *supra* note 4, at 397–98.

[169] *Id.*