

*Commentary***Sex, Gender, and Pharmaceutical Politics: From Drug Development to Marketing**Jill A. Fisher, PhD¹; and Lorna M. Ronald, PhD²¹Center for Biomedical Ethics & Society, Vanderbilt University, Nashville, Tennessee; and ²Interdisciplinary Studies Program, John Jay College (City University of New York), New York, New York**ABSTRACT**

Background: Biological sex differences and sociocultural gender norms affect the provision of health care products and services, but there has been little explicit analysis of the impact of sex differences and gender norms on the regulation of pharmaceutical development and marketing.

Objectives: This article provides an overview of the regulation of pharmaceuticals and examines the ways that regulatory agencies account for sex and gender in their review of scientific data and marketing materials.

Methods: The primary focus is on the US context, but information is also included about regulatory models in Europe, Canada, and Japan for comparative purposes. Specific examples show how sex differences and gender norms influence scientific and policy decisions about pharmaceuticals.

Results: The United States and Canada were found to be the only countries that have explicit requirements to include women in clinical trials and to perform sex-based subgroup analysis on study results. The potential influence of politics on regulatory decisions may have led to an uneven application of standards, as seen through the examples of mifepristone (for abortion) and sildenafil citrate (for erectile dysfunction). Three detailed case studies illustrate the importance of considering sex and gender in pharmaceutical development and marketing: Phase I clinical trials; human papillomavirus quadrivalent vaccine; and tegaserod, a drug for irritable bowel syndrome.

Conclusions: Sex and gender play important roles in pharmaceutical regulation, from the design of clinical trials and the approval of new drugs to advertising and postmarketing surveillance. However, regulatory agencies pay insufficient attention to both biological sex differences and sociocultural gender norms. This disregard perpetuates inequalities by ignoring drug safety problems that predominate in women and by allowing misleading drug marketing that reinforces gender stereotypes. Recommendations have been made to improve the regulation of pharmaceuticals in regard to sex and gender. (*Gen Med.* 2010;7:357–370) © 2010 Excerpta Medica Inc.

Key words: pharmaceutical regulation, drug development, marketing, direct-to-consumer advertising, Phase I trials, HPV quadrivalent vaccine, tegaserod, mifepristone, sildenafil citrate.

INTRODUCTION

Pharmaceuticals are an important topic through which to explore sex and gender in health care. This article explores the interplay of gender and pharmaceutical regulation to illustrate how sex and gender differences in drug development and marketing emerge from biology and politics. The concept of “pharmaceutical politics” highlights the complex interaction of regulatory agencies with sociocultural and economic interests to shape the medicines that are available and our knowledge about them. To begin with, sex differences and gender norms affect both drug development and marketing. By “sex,” we mean the biological characteristics or differences between men and women. By “gender,” we mean the social and cultural norms associated with masculinity and femininity. Specifically, some pharmaceuticals are designed for only one sex, such as hormonal contraceptives for women and erectile dysfunction medications for men. Other pharmaceuticals are approved for use only in one sex, such as drugs to treat irritable bowel syndrome (IBS) in women. These often did not start out as single-sex products, but clinical trial data showed efficacy in just one sex. Beyond the drug approval process, many pharmaceuticals exhibit marked sex differences in their effectiveness or adverse-effect profiles that emerge during clinical use.¹ For instance, some drugs seem to work better in one sex. This is the case for selective serotonin reuptake inhibitors, a class of drugs utilized primarily to treat depression, which tend to be more effective in women than in men.² Other drugs cause more adverse drug reactions in women than in men. Specifically, the US Government Accountability Office (GAO) published a report in 2001 which found that of the 10 prescription drugs withdrawn from the market between 1997 and 2001, 8 drugs “posed greater health risks for women than for men” and 4 drugs “had more adverse events in women even though they were widely prescribed to both women and men.”³

In addition, social and cultural assumptions about gender shape how pharmaceuticals and medical conditions are marketed to patients. This is especially true in the United States, where direct-to-consumer advertising (DTCA) of pre-

scription drugs is permitted. DTCA frequently blurs the line between healthy and unhealthy, frames health in gendered ways, or minimizes the severity of disease or treatment regimens.^{4–15} For example, advertisements for the birth control pill Seasonale®* offer women “freedom” from menstruation, by promising only 4 periods a year (1 every 3 months).¹⁶ As another example, prior to a US Food and Drug Administration (FDA) warning letter sent on April 27, 2001, some antiretroviral drugs were advertised in gay magazines with hypermasculine images of men participating in sports, such as mountain climbing, which are misleading pictures of what can be a grueling medication regimen for HIV/AIDS patients.^{9,12,17}

Gender has also been incorporated into the industry technique of rebranding existing drugs as new therapies. To extend the patent protection on the chemical comprising its blockbuster antidepressant, Eli Lilly repackaged Prozac®† as a pill named Sarafem® to treat premenstrual dysphoric disorder (PMDD) in women.¹⁸ Although premenstrual symptoms are unheard of in many parts of the world, in the United States they became framed as a medical matter of malfunctioning female biology.¹⁹ Like earlier psychopharmaceuticals dubbed “mother’s little helpers,” Sarafem advertisements drew on gendered imagery of marital discord and frazzled motherhood that suggested the drug could be a pharmaceutical solution to women’s domestic problems.²⁰ This marketing campaign led to the FDA issuing a warning letter to Eli Lilly on the grounds that the advertisements blurred the line between clinically normal and abnormal behavior and trivialized PMDD.²¹

This article begins with an overview of the regulation of pharmaceuticals. While our primary focus is on the United States, we also include information about regulatory models in Europe, Canada, and Japan. We describe the ways in which sex, gender, and politics become woven into pharmaceutical regulation, especially with the inclusion of women in clinical trials and sex-based

*Trademark: Duramed Pharmaceuticals, Inc. (Pomona, New York).

†Trademark: Eli Lilly and Company (Indianapolis, Indiana).

analysis of study results. In addition, we describe the potential influence of politics on regulatory decisions that may have led to an uneven application of standards, as seen through the examples of mifepristone (for abortion) and sildenafil citrate (for erectile dysfunction). Next, we provide 3 detailed case studies that illustrate the importance of sex and gender in pharmaceutical development and marketing: Phase I clinical trials; human papillomavirus (HPV) quadrivalent vaccine; and tegaserod, a drug for IBS. Finally, we conclude by summarizing problems with and proposing solutions for the current system of pharmaceutical oversight in regard to sex and gender.

OVERVIEW OF PHARMACEUTICAL REGULATIONS

US Drug Regulation

Because the United States is the leading market for the consumption of prescription drugs worldwide, the pharmaceutical industry often prioritizes its drug development and marketing strategy according to the rules and guidelines outlined by the FDA. The FDA regulates how clinical trials are conducted, which drugs are approved for clinical use, and how pharmaceuticals are marketed. For pharmaceutical companies to bring their products to market, they must engage in lengthy research and development to prove that those new pharmaceuticals are safe and effective.²²

The process for transforming chemical molecules into pharmaceuticals happens in the laboratory through bench and animal research as well as in the clinic through human experimentation. As products advance through the stages of testing, companies submit data and proposed protocols to the FDA to ensure that the research complies with regulations and will generate the information the FDA eventually needs to approve the products. For instance, pharmaceutical companies need sufficient data from animal studies before they can begin human testing. In addition, companies must show that the products are safe in a limited number of humans before they can commence larger studies to test the products' effectiveness. FDA oversight aims to protect human subjects, but it also assists pharmaceutical companies throughout the regula-

tory process in an incremental way that ensures their eventual new drug applications will be complete. This has led to the criticism that the FDA treats the pharmaceutical industry, instead of the American public, as its partner or client, leading to weaker enforcement of existing regulations.²³

The United States is 1 of only 2 developed countries (the other is New Zealand) that allow consumer advertising of prescription drugs, and the FDA is also the agency responsible for regulating all industry marketing campaigns. In its oversight of DTCA, the FDA follows regulations written in the 1960s which state that advertising must be fairly balanced and neither false nor misleading.²⁴ Since 1997, when it changed its guidelines to facilitate DTCA, the FDA has enforced advertising regulations by sending warning letters that ask pharmaceutical companies to stop or alter unbalanced or misleading advertising campaigns.²⁵ However, these letters are usually sent several months after advertisements have already been printed or aired.⁷

Although drug development and marketing are regulated as separate processes, pharmaceutical companies often blur the line between the two.^{23,26} Through postmarketing trials, physicians receive financial incentives to give their patients new drugs and ask them to fill out surveys.²⁷ Unlike more robust Phase IV surveillance studies that serve to generate important information about the safety and effectiveness of drugs newly released on the market, the data generated from these postmarketing studies have limited scientific value, but companies know that patients often continue taking the same drug after the trial has ended and that physicians prescribe the drug to other patients.²³ More broadly, the market potential of prospective new pharmaceuticals strongly influences the therapeutic areas in which companies invest their drug development resources.²⁸

International Drug Regulation

While the United States may indeed be the pharmaceutical industry's most lucrative market, other regions of the world are important for its profits, so companies must navigate multiple regulatory systems. Pharmaceutical companies can

either apply to the European Medicines Agency (EMA), or they can apply to a member country for their drugs to become available throughout Europe by means of mutual recognition agreements. In general, approval times are faster for new drugs in Europe than they are in the United States. However, Europe also has a higher rate of market withdrawal of drugs than does the United States, for example, 12% in Great Britain compared with 3% in the United States.²⁹ This suggests that accelerating patients' access to new pharmaceuticals leads to more safety issues, and regulatory agencies must balance these competing pressures.

Canada, in contrast, historically has had a more conservative approach to drug regulation, approving drugs more slowly than the United States and therefore withdrawing fewer from the market for safety reasons. However, Canada's regulatory agency, the Therapeutics Products Directorate, has recently adopted aspects of both the American and European models, requiring pharmaceutical companies to pay user fees (like the United States) and harmonizing its requirements with the EMA. This change is facilitated by the International Conference on Harmonisation, which emphasizes speeding up the approval process even when safety concerns might emerge as a result.²⁹

Japan's Pharmaceutical and Medical Devices Agency (PMDA) is the most conservative pharmaceutical regulatory agency worldwide because of its compensation scheme and ethnicity requirements. Starting in 1979, the original purpose of drug oversight was to compensate victims; the government pays medical expenses, disability compensation, and death benefits for injuries and deaths resulting from prescription drug use.³⁰ In addition, to market their products in Japan, pharmaceutical companies were required until 2007 to complete all their clinical studies in Japan on ethnic Japanese subjects. Now, the PMDA allows pharmaceutical companies to complete small-scale "bridging studies" using ethnic Japanese subjects worldwide to confirm that Japanese bodies metabolize the drugs similarly to original trial subjects' bodies.³¹ This recent change is expected to speed up drug approval times dramatically in Japan.

Although the FDA is often described as the most rigorous regulatory agency in the world, it focuses its review of new drug applications exclusively on safety and efficacy. In contrast, European nations and Canada also take into account comparative effectiveness and the cost of products when deciding whether to use drugs in their national health systems. While these measures do not keep drugs off the market, they do limit their adoption by health care providers. Prioritization of cost control and comparative effectiveness means that new drugs are evaluated against preexisting products, helping to determine their clinical utility rather than relying on the free market to do so.³² In 2009 as part of the American Recovery and Reinvestment Act, the United States earmarked significant sources of new funding for comparative effectiveness research through the Department of Health and Human Services, especially the National Institutes of Health and the Agency for Healthcare Research and Quality. It will be interesting to trace how this investment of research dollars might influence future health care policy in the United States.

Gender, Sex, and Regulation

National efforts to regulate drug development are beginning to include explicit attention to biological differences between men and women. In the 1980s, influenced by the women's health and HIV/AIDS movements, the US regulatory apparatus began not only to lift restrictions on women's participation in clinical trials, but also to incorporate requirements for medical research to include diverse populations and document differences based on sex and race/ethnicity.³³ Whereas federal funding mandates the inclusion of women and minorities in clinical research, private-sector research is regulated primarily through applications to the FDA for marketing new drugs or devices. Changes to FDA requirements were made in the late 1980s and early 1990s that lifted restrictions on women's participation in clinical trials and obliged companies to analyze clinical trial data by sex. Moreover, these requirements apply to marketing as well as to product labeling, which must include any sex-based differences that might influence the prescription decisions physicians and patients make.¹ Despite

these requirements, pharmaceutical companies often fail to include information on sex differences in their new drug applications, and the FDA fails to enforce its requirements before approving new drugs.³⁴ This effectively means that potential sex differences often remain unknown.

Canada is the only other country to have a regulatory approach to sex-based analysis of data from clinical trials which is similar to that of the United States. Beginning in 1996, it has required the inclusion of representative numbers of women in clinical trials followed by subgroup analysis. In contrast, the European Union and Japan have no such mandates. The Medicines and Healthcare Products Regulatory Agency in the United Kingdom explicitly encourages, but does not require, the inclusion of women in clinical trials.³³

GENDER POLITICS IN FDA OVERSIGHT

Like most government activities, the approval of new drugs is a political process.³⁵ Despite the institutional infrastructure and scientific processes in place at the FDA, broader politics, including gender politics, can influence the outcome of drug applications. The most striking cases are mifepristone and sildenafil citrate, which together tell quite different stories about the FDA approval of pharmaceuticals.³⁶

Mifepristone, initially known as RU-486, is a pharmaceutical that induces abortion. Evidence that mifepristone was both safe and effective was available in the late 1980s when it was approved in France, but the FDA requested that additional studies be conducted.³⁶ After these data were submitted, the FDA deemed in 1996 that the drug was both safe and effective, but delayed approving it by stipulating that additional label and manufacturing information was necessary before the product could go to market.³⁷ An additional 3-month delay occurred when the supplier of the bulk material changed, and the FDA requested supplementary data to ensure the stability and quality of the product. Mifepristone eventually received approval in 2000.

Given the political clout of antiabortion groups in the United States, mifepristone was seen by many members of Congress as very threatening

because this pharmaceutical has the potential to increase the availability of abortions.³⁷ To address this concern, the FDA mandated that mifepristone would not be available through a prescription at pharmacies but only through specially qualified licensed physicians, effectively limiting its use.³⁶ For the past 20 years, mifepristone has remained a politically controversial drug. There have been numerous (unsuccessful) bills proposed that would pass laws banning or restricting the use of mifepristone, and its approval and oversight have been the subject of Congressional investigation.³⁸

The case of sildenafil citrate (Viagra®*) is quite different. The FDA classified the drug to treat erectile dysfunction as “a major advance in treatment” so that it was eligible for priority review. The FDA granted approval of the product in 1998, less than 6 months after it received the application, at a time when most drugs took well over a year to receive approval. By the end of the year, the adverse-effect profile of sildenafil citrate was becoming increasingly a cause for concern, and the FDA required the manufacturer to issue a warning letter to physicians. Within just several months of the drug’s availability on the market, 242 deaths were linked to the drug, 130 of which were in the United States.³⁹ Moreover, the approved FDA label for sildenafil citrate has changed substantially between the years 1998 and 2008 to include passages from postmarketing experience about the possibility of heart failure as a result of taking the drug. Simultaneously, marketing for sildenafil citrate has broadened the drug’s use from an impotence treatment to erectile *enhancement*.⁴⁰ While there are serious risks of taking sildenafil citrate and the health benefits of this drug for this condition are limited, drug therapy for erectile dysfunction is not politically controversial, and there has been little political will to restrict the use of sildenafil citrate or to remove it from the market.

These 2 cases illustrate how sociocultural norms about gender can determine the availability of pharmaceuticals. Regardless of how innovative, safe, or effective the 2 products are, politics pre-

*Trademark: Pfizer Inc. (New York, New York).

vailed in keeping mifepristone off the US market for more than a decade. On the surface, it appears that it is simply abortion politics that influenced mifepristone's slow progress through the FDA approval process. At a deeper level, it can be read as gender politics, because gender norms construct promiscuity as problematic in women, but not in men. Mifepristone, similar to hormonal contraceptives, raises alarms that it will enable women's promiscuity.³⁶ In contrast, sildenafil citrate did not raise alarms about men's promiscuity. Gender politics thus allowed for the rapid approval of sildenafil citrate for the US market.⁴⁰ In other words, these cases show that gender politics do not operate only in the assessment of risks, benefits, and value of a product designed for women, but also in the review of a therapy for men.

INTERACTION OF GENDER, SEX, AND PHARMACEUTICAL POLITICS: CASE STUDIES

Underrepresentation of Women in Phase I Clinical Trials

The first stage of testing new pharmaceuticals in humans is referred to as *Phase I clinical trials*. These trials usually commence after sufficient data have been generated from animal studies to indicate to researchers that an investigational product is reasonably safe and appears promising as a therapeutic. The purpose of these studies is to test the safety of the drugs and to establish appropriate doses that can be given to humans. Establishing dosage for each drug is usually predicated on the idea that the dose should be as high as the human body will tolerate—before the adverse effects become too burdensome or dangerous for the majority of subjects. Multiple Phase I trials in which doses are sequentially escalated are necessary for companies to have enough data to understand the adverse-effect profile of each drug and to settle on the dose of the drug to be used in the next stage of clinical testing. Phase I studies are also known as *First-in-Man clinical trials*. Although this term employs the word “man” in a universal way to indicate the move from animal to human testing, its gendered connotation is apt. The vast majority of human subjects in these safety studies—approximately 70%—are men.⁴¹

The underrepresentation of women in Phase I clinical trials has several causes. Historical modes of paternalism assumed women needed additional protection in medical research. For example, from 1977 to 1993, the FDA banned “women of child-bearing potential” from early-phase clinical trials.⁴² The ban's purpose was to protect fetuses from exposure to investigational drugs that carried unknown risks, especially those that might be teratogenic. While limiting the participation of pregnant women in clinical trials may certainly be an appropriate way to minimize harm to the fetus, the broader ban on women's inclusion was based on the model that women are always potentially pregnant. Historically, the protection of hypothetical fetuses took priority over scientific knowledge about possible sex differences in the safety of new pharmaceuticals.

Today, companies often explicitly exclude women who are taking hormonal contraceptives from participation in Phase I studies. At times, this prohibition is linked to the companies' desire to include only healthy subjects who are not taking any prescription medications, but frequently there is a specific concern that contraceptives could change the absorption of the investigational drug or its adverse-effect profile. Men, in spite of their naturally occurring hormone cycles, are considered to be biologically static, and therefore are treated as the norm in science and medicine.⁴³

Another important contributor to the low participation of women in Phase I studies is the structure of the clinical trials. Because these are safety studies in which the effects in humans are unknown, the protocols are predominantly in-patient confinement studies.⁴⁴ Although some of these studies are completed in a weekend, others require human subjects to check in to the testing facility for up to 4-week stints. These studies are simply not compatible with many women's lives, given that women tend to be the primary caretakers of children and elderly parents. Thus, women may be excluded from studies because they cannot devote the same amount of time to participation that men can.

Regardless of the factors creating a gender imbalance in the enrollment rates of men and

women in Phase I studies, the effects of it are striking, especially as they reverberate beyond drug development to everyday clinical practice.⁴⁵ For instance, women are 1.6 times more likely to develop adverse drug reactions than are men, based on how drugs are absorbed, metabolized, and eliminated; in addition, women's reactions tend to be more severe and serious than are men's.^{46,47} Many researchers attribute these differences to women's lower body weight, smaller organ size, and higher percentage of body fat.⁴⁸

According to the FDA, differences in reactions to pharmaceuticals that occur between the sexes are relatively uncommon, with only 20% of the drugs the agency reviews indicating physiological differences between men and women.¹ However, a 2001 GAO report criticized the FDA for poor enforcement, citing evidence that almost 40% of the studies submitted to the FDA fail to reveal the sex of participants and 33% fail to present available safety data according to sex.³⁴ The GAO found this oversight particularly troubling in light of an earlier investigation which revealed that 8 of the 10 drugs removed from the market due to safety concerns between 1997 and 2000 posed greater health risks for women than for men.³

Safety concerns like these emerged only after the drugs had been approved by the FDA and were widely available to patients. This points to the need to more thoroughly understand the effects on men and women while these drugs are still under development. Because women are under-represented in Phase I studies, the scientific and

clinical knowledge that the medical community has about new drugs is dangerously limited. Conducting dosing studies on men skews the established dose of pharmaceuticals to amounts that may not be as well tolerated by women's bodies. The issue, however, goes beyond a simple one of sex; clinical trials need to include a diverse spectrum of human participants so that the adverse-effect profiles of new drugs can be known according to sex, age, body weight, and other important factors.^{49,50} The goal of the FDA should not be to work with pharmaceutical companies to bring their products to market as quickly as possible, but to provide and enforce policies to ensure that medical providers have a robust knowledge base to draw from when making decisions for their patients.

Human Papillomavirus Quadrivalent Vaccine

HPV is the most common sexually transmitted infection worldwide, contracted by most women shortly after the beginning of sexual relations. In the United States, HPV infects as many as four fifths of women as well as two thirds of men during their lifetime.⁵¹ Most cases of HPV are benign for those with fully functioning immune systems, but both women and men can suffer serious consequences of HPV infection. HPV is responsible for genital warts and various cancers, most famously, cervical cancer, but also oral, anal, and penile cancers (**Table I**).⁵²

The connection between HPV and cervical cancer was shown in the early 1980s.⁵³ Although

Table I. Worldwide cancers attributable to human papillomavirus infection.

Site	Total Cancers	Attributable Fraction, %	Attributable Cancers	Percentage of All Cancer
Cervix	492,800	100	492,800	4.5
Mouth	274,100	3	8200	0.1
Head and neck	52,100	12	6300	0.1
Vulva/vagina	40,000	40	16,000	0.2
Anus	30,400	90	27,400	0.2
Penis	26,300	40	10,500	0.1
All sites	10,843,600	–	561,200	5.2

Adapted from Parkin with permission.⁵²

cervical cancer is an outcome of HPV, it is by no means the case that HPV in women inexorably leads to cervical cancer. In fact, healthy women largely fight off HPV as well as the precursors to cervical cancers, lesions known as cervical intra-epithelial neoplasia (CIN) 1, 2, and 3. When the body's immune system does not fight off the lesions, Pap screening (Papanicolaou smear) can discover them and they can be removed. However, without adequate access to health care, women in developing countries and poor (often minority) women in the United States still suffer from cervical cancer that could have been prevented by regular screening (**Table II**).⁵²

Men can also be affected by HPV infection and its related ailments. In particular, men who have sex with men (MSM) suffer disproportionately from anal cancer, which is predominantly caused by HPV infection. Indeed, in the United States, the rate of anal cancer in MSM rivals the rate of cervical cancer seen in women prior to the introduction of routine Pap screening in 1960.⁵⁴ Currently, men do not have access to screening tests, and many are reluctant to utilize available health services, which may be amplified in the case of anal examination because of the fear of stigma for MSM.

Despite the broader risks of HPV, when Merck & Co., Inc. introduced the HPV quadrivalent vaccine to the United States in 2006, it was marketed primarily as a cervical cancer vaccine for girls and young women.⁵⁵ The clinical trials did not use cervical cancer as an end point, however, but instead used CIN lesions. This end point was approved by the FDA in November 2001 for 2 reasons: not only would demonstrating effectiveness against cervical cancer require a lengthy trial, but it would also mean denying patients the standard of care, because CIN lesions are removable.⁵⁶ Because of the focus on cervical cancer, the main efficacy studies included 16- to 26-year-old girls and women. The safety studies included both sexes but limited the age of subjects: female participants were aged 9 to 26 years, whereas male participants were aged 9 to 15 years.

Merck's head researcher on the project argued that these ages were chosen on the basis of "those

Table II. Cervical cancer attributable to human papilloma virus infection.

	Cervical Cancers	Percentage of All Cancer
Developing countries	409,400	7.0
Developed countries	83,400	1.7

Adapted from Parkin with permission.⁵²

that would benefit most from administration of a prophylactic HPV vaccine."⁵⁶ Even though the main efficacy studies did not, in this case, include boys and men, this Merck researcher also argued in favor of vaccinating both girls and boys. The reasons he provided were that "vaccine coverage in girls is going to be incomplete" and "men transmit HPV to women." Drawing on the example of rubella, he suggested that gender-neutral vaccination will more effectively reduce the rates of cervical cancer. Other researchers have agreed that men should be vaccinated as an additional means to prevent disease in women.⁵⁷ Yet, this rationale does not take into account the risks that HPV infection poses to men, especially MSM who are at heightened risk of HPV-related anal cancer. In late 2009, Merck sought and obtained FDA approval to market the vaccine to males (aged 9–26 years) for the prevention of genital warts caused by HPV; nonetheless, Merck has not yet promoted its cancer prevention potential for males.

Gender politics surrounding the HPV quadrivalent vaccine are most visible when examining how it has been marketed as Gardasil* to the US public. Avoiding depictions and discussion of sex and sexual transmission, the vaccine has primarily been marketed by mobilizing female empowerment rhetoric about cancer prevention. In the advertisements, young women in their twenties stand confidently, declaring that they want to be "one less" incident of cervical cancer and explaining "I chose to get vaccinated because..." As is frequently the case with empowerment rhetoric employed in health care contexts, "empower-

*Trademark: Merck & Co., Inc. (Whitehouse Station, New Jersey).

ment” seems to be achieved solely as the result of medical choices.⁵⁸ In this example, the message is that girls should protect themselves from cervical cancer with the vaccine—not through sex education or practicing safer sex. Though it is marketed as a cervical cancer vaccine, it has brewed controversy in the United States because the vaccine cannot be separated from debates about sex education,⁵⁵ and this will likely intensify with the marketing of the vaccine to prevent genital warts in males. While Merck was perhaps aiming to avoid this controversy, by not tackling it head on the company neglected key issues of public health. Not addressing sexual activity means leaving out all the risks of HPV to both male and female partners, regardless of their sexual orientation.

Irritable Bowel Syndrome and Tegaserod

IBS is a chronic condition that causes abdominal pain along with persistent diarrhea, constipation, or both. Its symptoms prevent sufferers from everyday activities, as they feel the need to limit the foods they eat and remain close to a lavatory. Foods that act as triggers include heavy, fatty foods; chocolate; alcohol; and carbonated drinks. In addition, stress can worsen IBS symptoms. Relatively little is known about what causes IBS, but the facts that women’s symptoms worsen during menstruation and that men are diagnosed less often than women have led some experts to point to hormonal causes.^{59–63} In particular, estrogen and progesterone may increase abdominal pain, and testosterone may have a protective effect. This fits with the idea that IBS is a “woman’s disease,” a common misconception that is reinforced by the development and marketing of IBS drugs for women only.

Diagnoses of IBS are more common among women than men in the United States and Western Europe.⁶⁴ One explanation for this difference lies in the general unwillingness of men to access health services or to let others know they are experiencing pain or discomfort.⁶⁵ However, recent research indicates that men may suffer equally and even access health services for IBS symptoms at the same rate as do women, but do not receive IBS diagnoses from their doctors.⁶⁶ This sex dispar-

ity does not exist in all other parts of the world, as **Table III** shows.⁶⁴ The sex gap in the United States and Europe has made it difficult to recruit men as research participants and to perform studies that assess the extent to which the different incidence in men and women is due to biological factors or the gendered nature of the disease.⁶⁷ Likewise, it has been difficult to prove drug efficacy in men without sufficient male clinical trial subjects.

Along with the management of IBS through dietary restrictions and stress reduction, several drug therapies have been developed that alleviate the symptoms of IBS. Recently, researchers have explored the connections between the brain and the gut and, following new understandings about the role of serotonin in both, 2 drugs were developed in the 1990s for IBS. First, alosetron was developed for diarrhea-predominant IBS in women. This is the more common form of IBS in men, but the drug was not found to be effective in this subgroup. Alosetron was approved by the FDA in February 2000, undeterred by the agency’s awareness that it may cause ischemic colitis, an enlargement of the large intestine.⁶⁸ It was voluntarily

Table III. Worldwide prevalence and gender distribution of irritable bowel syndrome.

Country	Prevalence (%)	Female-to-Male Ratio
United Kingdom	22.0	2.14
United States	17.0	2.00*
Hong Kong	17.0	0.99
Norway	16.2	1.04
Australia	13.6	2.01
Canada	13.5	1.75
China	11.5	1.25
Singapore	11.0	1.21
Spain	10.3	2.42
India	7.5	0.85
Korea	6.6	0.85
Japan	6.1	1.73
Iran	3.4	0.93

*Indicates an estimate derived from author’s discussion of overall prevalence in the United States.
Adapted from Gwee with permission.⁶⁴

withdrawn from the market in November 2000 following reports of severe gastrointestinal adverse events, including the death of 5 women taking the drug.⁶⁹ In June 2002, the FDA approved its reentry to the market under restricted conditions. Critics have suggested that the FDA's willingness to return the drug to the market shows the extent to which the agency serves the interests of industry.^{23,69}

In July 2002, the FDA approved another drug for women to treat IBS with constipation. Tegaserod (Zelnorm[®]) had been developed by the Swiss pharmaceutical company Novartis International AG. The Swiss drug regulatory agency, Swissmedic, had approved tegaserod in 2001. Lacking sufficient data for its safety and efficacy in men, both Swissmedic and the FDA approved tegaserod for IBS with constipation in women only. Later, the FDA allowed for its extension to men for the related condition of chronic constipation. This was based on 2 clinical trials in which 86% and 90% of the respective study populations were female.⁷⁰ Notably, some questions were raised during FDA hearings about the appropriateness of approving tegaserod for men with chronic constipation, given the paucity of male clinical trial subjects and concern about extrapolating study results from females to males.^{70,71}

After the US approval of tegaserod, Novartis began an intensive marketing campaign that featured women's bare abdomens with words written in black marker such as "Yes, there's help," "I'm feeling better," and "Ask your doctor." The advertising thus steered clear of the unsavory aspects of the condition by focusing instead on attractive young female bodies. Although IBS with chronic constipation is common among all age groups—and can worsen during menopause—these advertisements featured attractive young bodies of thin, primarily white, women in their twenties. In addition, newspaper advertisements were designed that included disease promotion campaigns for IBS itself, which gave information that "her pain and suffering are over ... in just three days," and thus overstated the efficacy of tegaserod.⁷² Because of limitations to FDA enforcement of advertising regulations, however, the warning letter was issued 3-1/2 months after the appearance of the advertisements it referenced. During these 3 months,

there was a substantial increase in doctor visits and IBS diagnoses.⁷³

In March 2007, less than 5 years after the FDA approved tegaserod, the agency asked Novartis to remove the drug from the market. A Swiss government meta-analysis of 29 trials had found an increased risk of adverse events—specifically, 13 cases of heart attacks, stroke, and angina.⁷⁴ Although tegaserod is a chemical that can bind to receptors not only in the gut but also in the heart, clinical trials had not shown any cardiac adverse effects. In the larger population, however, the drug had increased the risk of heart attacks. Given the fact that it did not consider IBS to be a serious condition, the FDA decided, along with other regulatory agencies including Health Canada, that the risk of heart attack was too great.

CONCLUSIONS

Sex and gender play a role in every stage of pharmaceutical regulation, from the design of clinical trials and the approval of new drugs to advertising and postmarketing surveillance. However, regulatory agencies pay insufficient attention to meaningful differences between women and men in terms of both sex and gender. This disregard, in our view, perpetuates inequalities by neglecting drug safety problems that predominate in one sex and by allowing misleading drug marketing that reinforces gender stereotypes.^{34,75} Clinical trials, for example, frequently lack an even composition of men and women. The first stage of testing drugs on humans, Phase I, is described as "First-in-Man," a phrase that is often literally true. Although some steps have been taken to include women, most drugs are tested for safety primarily on men, which is problematic because women often experience more severe adverse effects and may require lower doses. Pharmaceutical companies should be required to include representative populations in Phase I studies so that the drugs that are brought to market are safer for the patients consuming them.

In contrast to most Phase I trials, the examples of the HPV quadrivalent vaccine and tegaserod show that some clinical trials for effectiveness (known as *Phase III*) use few male subjects. In the case of the HPV vaccine, studies initially focused

on cervical cancer precursors rather than the range of conditions that HPV causes. For marketing reasons, one particular cancer in women took precedence over other HPV-caused diseases, which are less prevalent in men and women but nonetheless significant.⁵² The preponderance of data about the drug's effects on women and the virtual absence of data about effects on men hinder public health efforts to tackle HPV. Similarly, tegaserod was approved for IBS in women only. In this case, the rationale was not that men are unaffected by IBS or that the drug was ineffective in men, but simply that it was difficult to find male research subjects.⁷¹ Although the drug was subsequently approved for chronic constipation in both sexes, it is interesting to note that there was discussion within the FDA regarding the applicability of women's trial results to men. This indicates a double standard that is operating, wherein regulators do not question the generalizability of data derived from male participants but question the applicability of data from women to men. To enable both men and women to benefit safely from new pharmaceuticals, standards need to be applied symmetrically so that one sex is not considered the norm to which the other is held.

Beyond representation in clinical trials, regulatory institutions need to attend to sex and gender

politics in sales and marketing (**Table IV**). Ideally, this should include a critical understanding of the way that pharmaceutical companies use gender to construct disease and disease markets. As the Sarafem example at the outset of this article shows, the current system of pharmaceutical regulation allows for companies to create new brands without inventing new products.^{19,23} Critical attention to gender could help to reveal contestations behind disease categories like PMDD and strengthen the FDA's ability to evaluate advertising.

Fundamental challenges remain, however. Inadequacies with current drug regulation restrict the possibilities of making pharmaceutical oversight fair and effective for everyone. FDA oversight of pharmaceutical advertising has little value because of the delay between the start of a marketing campaign and the sending of a warning letter. Current standards for proof of safety and efficacy neglect to compare investigational products against the standard of care, which means that new drugs may be no more effective and possibly more harmful than the existing treatment options. Both women's and men's health are more likely to be endangered when regulatory bodies fail to engage these issues. Meaningful change, therefore, requires that government agencies prioritize public health

Table IV. Attending to sex and gender at every stage.

Stages of the Pharmaceutical Life Cycle	Actors Who Need to Pay Attention to Sex and Gender
Invention of drug	Funding bodies
Definition of condition	Pharmaceutical companies
Safety trials	Clinical trial centers
Efficacy trials	Private and government insurers
Drug approval	Government regulators
Recommendations for use	Medical professionals
Insurance reimbursement	Together, these actors must pay attention to sex and gender in the design and implementation of each stage of the pharmaceutical life cycle, as well as to the policies governing each stage. Crucially, these policies must also be enforced.
Drug advertising to consumers	
Drug promotion to doctors	
Postmarketing trials	
Postmarketing surveillance	

over the industry's interest in bringing new drugs to market.

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