EXPERT REVIEWS

Adverse effects in women: implications for drug development and regulatory policies

Expert Rev. Clin. Pharmacol. 4(4), 453–466 (2011)

Ameeta Parekh[†1], Emmanuel O Fadiran[1], Kathleen Uhl[2] and Douglas C Throckmorton[2]

[1]Food and Drug Administration, Office of Women's Health, 10903 New Hampshire Avenue, Silver Spring, MD 10993, USA
[2]Food and Drug Administration, Center for Drug Evaluation and Research, Office of Medical Policy, 10903 New Hampshire Avenue, Silver Spring, MD 10993, USA
[†]Author for correspondence:
Tel.: +1 301 796 9445
Fax: +1 301 847 8604
ameeta.parekh@fda.hhs.gov

The requirement to establish safety of drugs prior to marketing has been in place since 1938 by the US Food, Drug and Cosmetic Act and is by no means a new concept. The efficacy regulations were enacted in 1962 via the Kefauver–Harris Amendment and the drug approval process has evolved thereafter. The assessment of safety and efficacy of drug products is made by pharmaceutical companies during drug development, which then goes through a regulatory review by the US FDA for the determination of market approval or nonapproval. The drug development and regulatory approval processes have endured close ongoing scrutiny by regulatory bodies, the public, US Congress and academic and private organizations and, as a result, have ensured continual refinement. Over the years, evidence has been emerging on varied drug responses in subgroup populations, and the underlying biology associated with age, race and sex as demographic variables have been examined. The resulting growing knowledge of disease burden, treatment response and disparate outcomes has generated opportunities to streamline and improve treatment outcomes in these populations. This article discusses the historical context of women's participation in clinical drug trials submitted to the FDA for regulatory review and approval purposes. The inadvertent consequences of women's exclusion or inadequate representation in past clinical trials and the evidentiary basis for understanding sex differences are also evaluated. Advances in the US regulatory processes to address treatment outcomes that are tied to the topic of this paper, specifically, adverse drug effects in women, are also discussed.

Keywords: drug development • exposure • response • safety • sex difference • women's health

A perceived need to protect specific populations in clinical research, such as women, is deeply rooted in the historical adverse experiences of the 1960s and 1970s following exposures to thalidomide [101] and diethylstilbesterol [1] and use of the Dalkon Shield [102]. The use of these medical products caused debilitating health outcomes for women and/or their offspring and led to an extremely cautious approach to including women in future clinical trials.

Although the US FDA's mission is to protect public health by ensuring safety, efficacy and security of human and veterinary drugs, biologics and medical devices ensuring the safety of foods, cosmetics and radiation-emitting products, and regulating tobacco products, the FDA also shares the responsibility for ensuring the safety of human subjects involved in clinical trials. The need to protect vulnerable populations during drug development was evident as the premise behind the FDA's 1977 Guidance entitled *General Considerations for Clinical Evaluation of Drugs* [103]. This guidance cautioned regarding unintended drug exposure in women of childbearing potential (WCBP) and advised that this population be excluded from the earliest dose-ranging studies in order to protect the fetus from inadvertent drug exposure. The guidance also specified that WCBP may be included in further studies once satisfactory safety information was generated from animal fertility and teratology studies and after adequate information on efficacy and safety was amassed from early clinical trials [103]. This guidance, however, was widely misinterpreted to mean exclusion of all women

 10.1586/ECP.11.29 ISSN 1751-2433

from all clinical trials and undoubtedly contributed to their inadequate representation or exclusion in many clinical trials conducted thereafter.

The basis for excluding WCBP from early-phase clinical studies was subsequently challenged in the early 1980s on ethical grounds. Patients' and women's health advocacy groups voiced disapproval of the FDA's guidance, arguing that this approach circumvented several principles of informed consent including:

- Women's autonomy to make independent decisions regarding trial participation;
- Women's judgment on balancing risk and benefits to their fetus;
- Women's ability and interest in contributing to the medical understanding of sex differences;
- The societal need for understanding how drugs work in a large proportion of the population – that is, women [2].

Other coincidental factors were also fueling the public disapproval of women's inadequate representation in clinical trials at this time. In the mid-1980s, a Public Health Services conference emphasized the need for basic research and understanding of diseases that were taking a toll on women's health, including breast and lung cancers, heart disease and reproductive issues [3]. An analysis by the FDA's Center for Drug Evaluation and Research of the New Drug Applications (NDAs) reviewed in 1982, 1988 and 1992 concluded that, although women were represented in the clinical trials for new drugs, they were under-represented in some therapeutic classes, such as cardiovascular disease [4]. A report by the General Accountability Office (GAO) in June 1990 reported that women were routinely excluded from medical research studies supported by federal funds [5]. In the late 1980s and early 1990s, national attention was drawn to the fact that women in the USA die of the same diseases as men, such as heart disease, cancer and stroke, and yet women were not being adequately studied in these disease areas [5]. AIDS was initially thought to be a disease primarily affecting men and, as a result, few trials were designed to include infected women. However, AIDS was rapidly becoming a major cause of death in women, which further fueled the national outcry on women's exclusion from clinical trials [6]. The burgeoning AIDS epidemic and the newly discovered antiviral drug treatments, as well as the rapid evolution of therapies for cancers, escalated the concern that women's access to new breakthrough treatments may be hampered if they were excluded or under-represented in clinical research [2,6]. In October 1992, the FDA and the Food and Drug Law Institute held a public meeting to discuss the restriction clause in the 1977 guidance, as well as the broad issue of women in clinical trials. The discussion concluded that inclusion of young women in clinical trials could contribute to a greater understanding of how new drugs worked in women. Inclusion of reasonable numbers of women in drug trials to ensure identification of clinically important sex differences was subsequently emphasized for future studies [4]. Other barriers to women's participation in clinical trials, such as the logistical and economic considerations, have also generated extensive discussion [104].

In retrospect, the heightened attention to women's adequate participation in clinical trials served as an important milestone in US history for studying sex differences in clinical research and has since led to accrual of information in both sexes.

Evidence of sex differences in drug exposure & response

Variability in treatment outcomes between patients could arise from differences in drug exposure and/or response [7–9]. Evaluating exposure (measured as systemic drug concentrations) and response differences resulting from demographic variables such as age, race and sex are now routinely examined during drug development for FDA regulatory review purposes and for dosage adjustment determination.

Drug exposure may vary between women and men owing to differences in absorption, distribution, metabolism and excretion and could lead to differences in drug response [10,11]. However, experimental differences in pharmacokinetics (PK) observed between men and women have frequently been attributed to bodyweight differences, and PK parameters recalculated with a bodyweight correction tend to account for most of the observed PK differences. Interestingly, most drugs are not administered on a mg/kg basis but as a fixed dose for all adult patients, potentially leading to higher doses and subsequently higher exposures in women due to their lower bodyweight compared with men.

The following examples of adverse outcomes in women have contributed to the mounting clinical evidence of sex differences and complement the regulatory advances on this topic. These examples provide a compelling case to study women and men during all phases of drug development. They demonstrate areas where we do not or cannot predict risk well and reinforce that sex differences should be studied throughout drug development. We must understand sex differences beyond the basic physiologic differences in order to optimize patient treatment outcomes.

Examples of exposure differences between men & women

Significant difference in drug exposure between men and women has been reported for ondansetron (Zofran®), a drug approved to prevent nausea and vomiting resulting from chemotherapy or in the postoperative setting [12]. The FDA-approved labeling for ondansetron also states that women have 1.5- to two-times the peak drug plasma concentrations and a lower oral clearance compared with men (Table 1); however, no dosage adjustment based on sex is recommended in the product labeling [105]. Although the label does not address clinical relevance of these sex differences in PK, similar lower oral clearances are reported in elderly patients and patients with mild-to-moderate hepatic impairment. No dosage adjustment is recommended in these patients either. This is based on comparable safety and efficacy in younger patients and in those 65 years of age and older in ondansetron clinical trials. The recommended adult dose of ondansetron is 24 mg administered before emetogenic chemotherapy or 16 mg before anesthesia and is not dosed on a mg/kg basis.

Table 1. Pharmacokinetics of ondansetron (Zofran®) in healthy volunteers†.

Age group (years)	Sex	Mean weight (kg)	Subjects (n)	Peak plasma concentration (ng/ml)	Systemic clearance (l/h/kg)
18–40	Male	69.0	6	26.2	0.403
	Female	62.7	5	42.7	0.354
61–74	Male	77.5	6	24.1	0.384
	Female	60.2	6	52.4	0.255

†Single 8-mg oral tablet.

Olanzapine (Zyprexa®) labeling, on the other hand, recommends lower doses in patients in whom higher exposures are anticipated. Olanzapine is an atypical antipsychotic approved for the treatment of schizophrenia and bipolar disorder. For schizophrenia, the starting dose is 5–10 mg/day with a target dose of 10 mg/day within several days [106]. However, given the treatment-related adverse events that are dose and exposure dependent, a lower dose is recommended in specific populations who may have higher plasma concentrations. For example, olanzapine clearance is lower in women than in men. Clearance is also lower in the elderly (≥65 years) than in subjects less than 65 years of age, resulting in higher plasma concentrations. Olanzapine is extensively metabolized before reaching the systemic circulation, and cytochrome *P450 1A2* has been identified as one of the enzymatic pathways of metabolism. This enzyme is induced by cigarette smoking and, as a result, olanzapine clearance is approximately 40% higher in smokers than in nonsmokers. Although each of these factors may not independently justify dosing adjustment, the combined effects of age, smoking status and patient's sex could lead to substantial PK differences in certain populations and increase the likelihood of adverse effects from higher exposures. The plasma concentrations in elderly nonsmoking females, for example, may be higher than those in young smoking males. The labeling for olanzapine recommends a lower starting dose of 5 mg daily for patients who exhibit a combination of factors (e.g., nonsmoking female patients ≥65 years of age) as higher plasma concentrations are expected in these patients [106].

Examples of response differences between men & women

QTc prolongation & Torsades de Pointes

The QTc interval is a measure of cardiac repolarization and is readily monitored through electrocardiograms (ECGs). Torsades de Pointes (TdP) is a potentially fatal polymorphic ventricular tachycardia associated with QTc interval prolongation. Women have been associated with a longer baseline QTc interval and have an increased propensity for experiencing drug-induced TdP [13]. This higher cardiac risk in women has been reported for many drugs.

Significant differences in both drug exposure and response between men and women have been reported for dofetilide (Tikosyn®), a potassium channel-blocking antiarrhythmic drug approved for the maintenance of normal sinus rhythm in patients with atrial fibrillation/atrial flutter of greater than 1 week duration who have been converted to normal sinus rhythm, and for the conversion of atrial fibrillation and atrial flutter to normal sinus rhythm. Dofetilide is primarily renally excreted and reductions in creatinine clearance in patients result in higher dofetilide exposures. Dofetilide can cause serious ventricular arrhythmia, primarily TdP, which is related to an increase in systemic exposure. Women's systemic exposure to dofetilide is 14–22% higher after correcting for bodyweight and creatinine clearance [14]. Safety data during the clinical drug development program showed that the risk of TdP in women was approximately three-times the risk in men and the risk for TdP is directly related to dofetilide plasma concentration and dose. This is reflected in Figure 1 [107]. Consequently, the FDA-approved labeling for dofetilide warns of TdP-type ventricular tachycardia with QTc interval prolongation and recommends an individualized dosing algorithm to include obtaining baseline QTc interval assessment and an estimate of patient's creatinine clearance. Since the latter is estimated using bodyweight, age and a correction factor for women, dose estimates in women are typically lower. The usual recommended dose of dofetilide is 500 µg twice daily but modification of doses based on the patient's creatinine clearance and baseline QTc measurements take into consideration the sex-specific dosing criteria of this drug [107]. Unlike in the cases of ondansetron and olanzepine, where the sex differences are primarily due to PK differences, higher dofetilide exposure in women due to lower creatinine clearance, combined with higher sensitivity and longer QTc interval at baseline, make women more vulnerable to drug-induced TdP, illustrating sex differences in PK as well as pharmacodynamics (PD).

A higher risk for drug-induced QTc prolongation and TdP in women is not unique to dofetilide. An increased risk of TdP in women has been reported for the anti-arrhythmic drugs sotalol and quinidine. At equivalent doses of d-sotalol (the d-isomer of

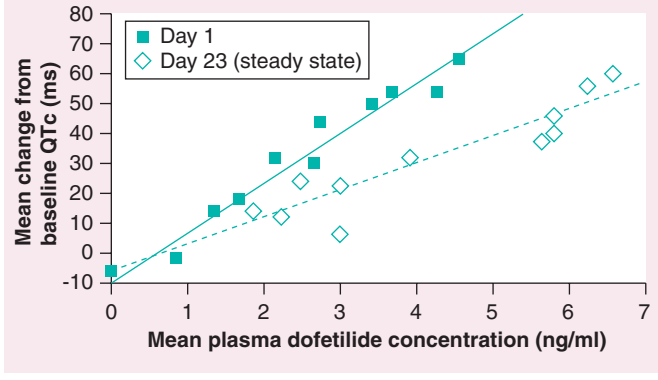

Figure 1. Mean QTc–concentration relationship for dofetilide in young volunteers over 24 days of Tikosyn® dosing.
Reproduced from [107].

sotalol) given to men and women, a greater QTc interval prolongation was observed in women compared with men [15]. PK of d-sotalol was similar in men and women and the greater QTc interval prolongation was attributed to higher baseline QTc values in women [15]. Another study, comparing d-sotalol with placebo in patients with prior myocardial infarction, noted that female sex was a major risk factor for excess mortality related to arrhythmias in the treatment group. This study was terminated early due to the higher mortality in women [16]. The labeling for Betapace® (dl-sotalol, the racemic mixture of d- and l-isomers) describes the dose-related increase in TdP potential with female sex being an additional risk factor. The label recommends that Betapace should only be administered after appropriate clinical assessment and the dosage must be individualized for each patient on the basis of therapeutic response and tolerance. Pro-arrhythmic events can occur at initiation of therapy and also with each upward dosage adjustment; therefore, doses should be increased in a hospital with facilities for cardiac rhythm monitoring and assessment [108]. Quinidine produces a larger QTc interval prolongation in women for the same plasma concentrations as men. This is shown in Table 2 where women (compared with men) have higher slope values for the relationship between quinidine concentrations and the corresponding QTc intervals. Both total and unbound quinidine concentrations show this trend [17]. As per the labeling, treatment initiation or dose adjustment in patients with known structural heart disease or other risk factors should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continuously available. The labeling also advises that patient monitoring be continued for 2–3 days after initiation of the regimen on which the patient will be discharged [109].

The 2001 GAO report entitled *'Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Risks for Women'* drew further attention to women's susceptibility to drug-induced QTc interval prolongation and the safety implications for women [110]. Upon the FDA's request, GAO identified prescription drug products withdrawn from the US market between January 1997 and December 2000 and examined which of the withdrawn drugs posed greater health risks for women than for men. This report concluded that eight of the ten prescription drugs withdrawn from the market during this time posed higher risks for women and four of the ten drugs withdrawn were implicated for TdP potential from drug-induced QTc interval prolongation (Table 3).

Several attempts have been made to elucidate the underlying mechanism for the greater sensitivity to QTc interval prolongation and TdP in women compared with men. Animal studies suggest that sex hormones may play a critical role in regulating cardiac repolarization [18]. In humans, baseline QTc assessments through puberty and the changes during the menstrual cycle have revealed that prepubertal baseline QTc is similar for both the sexes [17,19]. At puberty, testosterone exerts a protective effect in men through shortening of the baseline QTc intervals, with women's QTc remaining unchanged. Manifestation of this longer QTc interval for women at baseline is explained as one of the causes of physiological divergence in men and women leading to higher arrhythmia and TdP propensity in women [17,19,20].

Cardiovascular risk

Anti-thrombotic agents are typically used for the treatment of acute coronary syndrome or deep-vein thrombosis (DVT). These drugs have a narrow therapeutic range of optimal dosing, outside of which the efficacy or safety of the drugs may be compromised. Dosing strategies have been defined to minimize bleeding risks while maintaining efficacy by individualizing dosing needs for this class of drugs. These are based on bodyweight and renal function [21]. Yet, owing to complexities associated with dosing of anti-thrombotic agents, a higher bleeding risk in women has been observed. In a prospectively planned study with DVT patients on heparin, patients were evaluated for activated partial thromboplastin time (APTT) and heparin blood levels [22]. Dosing was rapidly adjusted to achieve therapeutic APTTs to minimize bleeding events in this study. The study showed that women achieve higher heparin blood levels for any given heparin dose and have a lower heparin dose requirement than men. Women required 17% less heparin than men to achieve therapeutic APTTs. Bodyweight is therefore a consideration in heparin dosing. Even after correcting for bodyweight, women of increasing age were associated with higher heparin blood levels than men, thereby increasing their susceptibility to excessive bleeding. This is an important clinical consideration in older women since coronary thrombosis and thromboembolism have been shown to increase with age [22]. A prospective observational analysis of non-ST segment elevation in an acute coronary syndrome patients' registry investigated associations between anti-thrombotic therapy dose (unfractionated heparin, low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors) and major health outcomes such as bleeding, in-hospital mortality and length of stay [21]. Relative to the dosing recommendations in product labeling, general dosing guidelines and recommendations in clinical trial publications, the study suggested that nearly 42% of the patients received excess anti-thrombotic drug doses. Women were more likely to receive doses in excess of those defined by the guidelines and significantly higher bleeding was associated with this excessive dosing [21]. In a separate

Table 2. Pharmacodynamic parameters for quinidine†.

Parameters measured	Women	Men	p-value
Baseline mean QTc interval, ms (mean ± SD)	407 ± 7	395 ± 9	<0.01
Slope ΔQTc versus total quinidine concentration (mean ± SE), ms/μg/ml	42.2 ± 3.4	29.3 ± 2.6	<0.001
Slope ΔQTc versus unbound quinidine concentration (mean ± SE), ms/μg/ml	194 ± 8	144 ± 9	<0.001

†Total and unbound quinidine.
SD: Standard deviation; SE: Standard error.

prospective clinical trial, patients undergoing percutaneous coronary intervention received an initial heparin bolus dose followed by either a glycoprotein IIb/IIIa inhibitor (abciximab) with low-dose weight-adjusted heparin or placebo with low-dose weight-adjusted heparin [23]. The study monitored both major bleeding events (defined as reduction of hemoglobin of more than 5 g/dl or any intracranial bleeding) and minor bleeding events (defined as observed blood loss with reduction in hemoglobin between 3 and 5 g/dl, hematuria or hematemesis). The rates of both major and minor bleeding events were higher in women on abciximab, even with low-dose weight-adjusted heparin, as compared with men. Women's minor bleeding events on placebo with weight-adjusted heparin were also higher than those seen in men [23].

An increased risk of hemorrhagic stroke in women, but not in men, was associated with phenylpropanolamine, a drug used for nasal decongestion as well as an appetite suppressant for weight control. This was concluded through several spontaneous reports to the FDA and through a case–control study of men and women with symptomatic subarachnoid or intracerebral hemorrhage conducted in 43 US hospitals. This safety concern was discussed with an FDA Nonprescription Drug Advisory Committee in October 2000 [111]. Subsequent to this meeting, the FDA issued a public health advisory regarding the increased risk of hemorrhagic stroke in women and took steps to remove phenylpropanolamine from all prescription and over-the-counter drug products [24,112].

Fracture risk

Higher fracture risk has been reported for women as compared with men during long-term use of hypoglycemic drugs of the thiazolidenedione class. A Diabetes Outcome Progression Trial (ADOPT) was a randomized controlled clinical trial in Type 2 diabetes patients comparing the efficacy and safety of rosiglitazone, a thiazolidinedione, with metformin and glyburide [25]. In ADOPT, all patients were titrated to the maximum effective daily dose of hypoglycemic drugs. Patients were well matched at baseline and the median duration of follow-up was 3.3 years (glyburide) and 4 years (rosiglitazone and metformin). This study concluded that long-term treatment with rosiglitazone was associated with an approximate doubling of bone fracture risk as compared with metformin and glyburide in women with Type 2 diabetes. The study showed no increased risk of fractures among men. Specifically, men's fracture risks were approximately 4% for rosiglitazone, 3.4% for metformin and 3.4% for glyburide, and the risks in women were 9.3% for rosiglitazone, 5.1% for metformin and 3.5% for glyburide. Further analysis in women showed that this trend for increased fracture risk with rosiglitazone occured in both premenopausal and postmenopausal women, manifested after a year of therapy and did not appear to be due to increased falls or accidental limb injury. The majority of the fractures occurred in the upper arm, hand and foot, locations that are not common for osteoporotic fractures. Drug labeling for rosiglitazone describes the higher fracture risks for female patients [113]. A higher incidence of nonvertebral fractures in women was also reported for pioglitazone, another thiazolidinedione hypoglycemic drug approved for Type 2 diabetes [26]. In a review of 19 double-blind randomized controlled trials of pioglitazone in diabetic patients where participants in the comparison group were given either a placebo or another diabetic drug (metformin or a sulfonylurea), an increased fracture risk was seen in women on the pioglitazone arm as compared with the comparator groups in the trials [26]. The duration of treatment varied from 16 weeks to 3.5 years. Among women, 2.6% of those in the pioglitazone group experienced fractures, compared with 1.7% in the comparator group. There was no apparent increase in fracture risk among men. The labeling information for pioglitazone reports that the fracture rates in women were twice as high in the pioglitazone group as compared with placebo in Type 2 diabetes patients at 3 years of follow-up in a randomized clinical trial and that no difference was observed in men [114]. The FDA-approved labeling for both rosiglitazone and pioglitazone

Table 3. Prescription drugs withdrawn from the US market (1997–2000).

Drug	Type of drug	Patient population	Primary health risk
Prescription drugs with evidence of greater health risks in women			
Pondimin®	Appetite suppressant	Women	Valvular heart disease
Redux®	Appetite suppressant	Women	Valvular heart disease
Rezulin®	Diabetic	Women	Liver failure
Lotronex®	Gastrointestinal	Women	Ischemic colitis
Seldane®	Antihistamine	Women and men	Torsades de Pointes
Posicor®	Cardiovascular	Women and men	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal®	Antihistamine	Women and men	Torsades de Pointes
Propulsid®	Gastrointestinal	Women and men	Torsades de Pointes
Prescription drugs without evidence of greater health risks in women			
Raxar®	Antibiotic	Women and men	Torsades de Pointes
Duract®	Analgesic and anesthetic	Women and men	Liver failure

advise that the fracture risk in treating female patients should be considered and attention should be given to maintaining bone health in accordance with current standards of care [113,114].

These aforementioned examples of adverse health outcomes associated with drug exposure or response in women have contributed to the growing evidence of sex differences. These examples reinforce the importance of understanding sex differences and complement the regulatory policies on assessing subgroup population differences in treatment outcomes described in the following section.

Evolving regulatory practices related to women's health

The drug-development enterprise is considered by some to comprise of three eras [27]. The first era, described to be that of safety requirements, was stimulated by the discovery that considerable harm can result from drugs if they are not adequately tested. The second era, that of efficacy requirements, resulted from the stimulus provided by the thalidomide experience that caused birth defects when used by pregnant women. The subsequent enactment of the Kefauver–Harris Amendment to the Food, Drug and Cosmetics Act of 1962 required drug manufacturers to show efficacy, in addition to safety, of their products. In addition, they were required to report adverse events to the FDA and to ensure that their advertisements to physicians discloses the risks, as well as the benefits, of their products [115]. The thalidomide experience also catalyzed new directions for regulatory review and drug approval through stricter regulation of the investigational steps of drug development. Adequate animal testing prior to human use, the Investigational New Drug (IND) development phases, human subject protection and the informed consent process were initiated by the FDA as some steps to demonstrate drug efficacy through controlled clinical trials [27]. The third era of drug development was described to be that of individualization of drug therapy that drew increased attention to response differences in subgroup populations. New regulations and guidances were developed at the FDA addressing clinical trial designs and data-analysis approaches in several populations. For example, the first of these was initiated in the 1980s and focused on addressing response differences in the elderly patients. This concept was subsequently broadened to other subgroup populations to include age, race and sex [27].

In 1993, the FDA issued the guidance '*Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*' reversing the earlier guidance of 1977 where WCBP were recommended to be excluded from the earliest dose-ranging studies [116,117]. The 1993 guidance emphasized the importance of PK and PD assessments in women and analysis of safety and efficacy data by sex. In 1998, the FDA enforced regulatory requirements on reporting clinical data by age, race and sex through the amendments of the IND and NDA regulations (21 Code of Federal Regulations [CFR] 312.33 and 21 CFR 314.50). These regulations required that NDAs contain information on clinical trial participation as well as analysis of safety and efficacy by age, sex and racial subgroups, and also required IND annual reports to tabulate the number of participants enrolled according to age, race and sex. The *Amendment to Clinical Hold Regulations* published in 2000 allowed the FDA to stop IND studies for treatment of life-threatening diseases if women or men were excluded primarily due to their reproductive potential [118].

Regulatory attention was also directed towards other demographic factors, such as pediatric age groups and patients with underlying disease states, as evidenced by the development of guidance documents for various subgroup populations. Guidances and regulations were also published on format and content of prescription drug labeling, PK, PD, efficacy, dosing and adverse outcomes in subgroup populations including women [119,120]. Tables 4 & 5 list the relevant regulations and guidances regarding subgroup populations in clinical trials and the new labeling requirements.

The implementation of new processes, guidances and regulations paved new directions for understanding treatment and response differences between subgroup populations and communication of this information through labeling. The next section of the paper discusses how women's participation in clinical trials has progressed over the years.

Participation of women in clinical trials

Traditionally, the drug-development process is conducted in various phases (Phase I, II and III) with the postmarket assessments continuing after drug approval (Phase IV). Early-phase clinical drug development typically generates data on dose tolerability in healthy volunteers and/or patients (Phase I). Proof of concept is established in Phases I and II and these phases subsequently

Table 4. US FDA regulations reflecting women's participation in drug studies and labeling.

Year	FDA regulation	Direction
1998	Investigational New Drug Applications and New Drug Applications (21 CFR 312.33 21 and CFR 314.50)	Required Investigational New Drug and New Drug Applications to tabulate on trial participation by subgroups and analysis of safety and efficacy data by sex, age and racial subgroups
2000	Clinical Hold for Products Intended for Life-Threatening Diseases (21 CFR 312.42)	Permits the FDA to stop Investigational New Drugs studies for treatment of a serious or life-threatening disease if women or men are excluded due to reproductive potential
2007	Specific requirements on content and format of labeling for human prescription drug and biological products (21 CFR 201.57)	The requirements in this section apply to prescription drug products and must be implemented as contents of drug labeling

CFR: Code of Federal Regulations.

advance to the principal controlled studies (Phases II and III) wherein dose response for efficacy, safety, dosing regimen and common side effects in the study populations are determined. One would envision that the heightened awareness of subgroup population differences and the resulting need to study various patient demographic characteristics would favorably affect their inclusion in clinical trials. The participation of women in various clinical trial phases and analysis of outcomes for sex differences has been assessed by some stakeholders and is summarized here.

In 1992, the GAO published a report on the extent of women's participation in Phase II/III prescription drug trials for drugs that were approved by the FDA between January 1988 and June 1991 [121]. This report also assessed whether or not sex-based analyses were performed in these NDA clinical trials. A similar assessment was carried out by GAO in 2001 for drugs approved from August 1998 to 31 December 2000 [122]. These studies showed that women's participation in late-phase clinical trials had, on average, improved over the evaluated years, albeit certain therapeutic areas reflected lower participation. Women's participation in Phase II and III trials was approximately 44% in the 1992 GAO report, while it exceeded 50% in the 2001 GAO report. An internal FDA review of new molecular entity drugs (NMEs) approved during 1995–1999 showed that participation of women and men was 48 and 52%, respectively [123]. A more recent survey of NMEs approved during 2000–2002 also showed an overall equal participation of men and women in late-phase clinical trials [28,121,122].

Participation of women has been relatively low in Phase I trials where dose tolerability, clinical pharmacology assessments, dose-related side effects and early evidence of efficacy are frequently determined. For NDAs submitted during 1995–2002, three studies reported women's participation in the range of 22–25% [28,122,123]. For NDAs submitted during 2006–2007, one study reported women's participation at 31% [29].

In addition to participation, analysis of clinical trial data for sex differences in treatment response is vital for a meaningful understanding of dosing adjustment needs based on response differences. The 1992 GAO report concluded that approximately 47% of NDAs approved from January 1988 to June 1991 analyzed the clinical trial data for sex differences [121]. Sex-specific analyses were approximately 70% for drugs approved from August 1998 to December 31 2000 and NMEs approved during 2000–2002 [28]. While a precise comparison is not feasible due to the different clinical trial phases and sources of information incorporated in the analyses (i.e., sponsor- or FDA reviewer-performed analyses), a general trend showing an increase in sex-specific analysis for efficacy, safety or PK is evident.

Regulatory guidances and regulations have drawn attention to the importance of including demographic subgroups in clinical trials and reports have shown improved participation of women and sex-based analysis in drug applications subjected to regulatory review. Some recent initiatives that complement the rigorous premarket drug-development and approval processes through postmarket assessments of drug product performance are discussed in the next section. A recent labeling regulation that attempts to clearly communicate risk to healthcare providers is also discussed.

Landmark initiatives & legislation: sex differences

Despite the robust premarket review and approval processes, adverse events inevitably emerge during the postmarket period of the drug products' life cycles [124]. These adverse events are often rare, may occur with long drug product latency or result from the real-world population of comorbidities, concomitant medications and diverse demographics not seen or studied during drug development. While the FDA's postmarketing surveillance system augments its existing data on the risks and benefits of FDA-regulated products, these data are limited. Much of the additional information resides with industry, academia and healthcare systems, and an active involvement of all healthcare stakeholders is essential to improve drug safety. The FDA has leveraged such collaborative partnerships among all stakeholders to help generate additional understanding of drug product safety from existing pools of information. These added resources complement the existing knowledge base at the FDA to address important public health issues such as sex differences in treatment outcomes. Some specific initiatives on assessing drug product safety in women through such partnerships are discussed in the following section.

The FDA critical path initiative

Biomedical research has benefited from a surge of innovations in recent years in the areas of genomics, proteomics, advanced medical imaging and biomarkers for safety and efficacy. However, there have been concerns that these advances in basic sciences have not yielded more effective, affordable and safe medical products for patients and that the soaring cost of product development is not reflected in the numbers of innovations reaching patient populations [30]. This disconnect between basic sciences and an equivalent impact on approval of new therapies provided the impetus for the launch of the FDA's Critical Path Initiative (CPI) in 2004 [125,126]. The primary goal of the CPI is to modernize the clinical trial enterprise and to apply efficient safety and efficacy tools to transform the way in which FDA-regulated products are developed, evaluated and manufactured. Owing to the integrative and multidisciplinary nature of the task, the FDA has fostered collaborations among academia, industry, federal agencies and nonprofit organizations through public–private partnerships (PPPs) and defined innovative programs aimed at fulfilling several unmet public health needs [31,127].

As discussed in previous sections, women's predisposition to drug-induced QTc interval prolongation has been documented as a safety risk for women. One of the PPPs started under the CPI is the Cardiac Safety Research Consortium (CSRC) [128]. Through the CSRC, public access has been enabled to thousands of previously proprietary ECG waveforms from QT studies housed in the FDA's ECG warehouse [129]. The source of these data are the matched ECG waveforms from human volunteers exposed to placebo or moxifloxacin, a positive control typically used in QT studies that provides a known safety signal of QT prolongation [130]. The available datasets will characterize key subgroup populations for variations in measurements such as

Table 5. US FDA guidances relevant to ensuring womens' and other subpopulations' participation in drug studies.

Year	Guidance	Direction
1988	Format and Content of the Clinical and Statistical Section of an Application	Recommended data analysis of safety, effectiveness and clinical pharmacology studies by sex, race and age
1989	Study of Drugs Likely to be Used in the Elderly	Recommended PK screen of Phase II/III trials and data analysis by age and sex
1993	Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs	Recommended PK and PD in women, PK screen as a tool to detect differences, analysis of safety and efficacy by sex
1998	Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (Draft 1998)	Intended to assist applicants planning to conduct PK studies in pediatric populations and addresses general considerations for conducting such studies so that drug and biological products can be labeled for pediatric use
1998	Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis and Impact on Dosing and Labeling	Recommended studies to assess the influence of renal impairment on the PK of an investigational drug
1999	Population Pharmacokinetics	Recommended extensive or sparse sampling in clinical trials to assess the influence of demographic variables
2003	Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis and Impact on Dosing and Labeling	Recommended studies to assess the influence of hepatic impairment on the PK and the PD of a drug, including therapeutic biological products
2005	Pharmacogenomic Data Submissions	Recommended when to submit pharmacogenomic data during the drug or biological drug product development and review processes, what format and content to provide for submissions and how and when the data will be used in regulatory decision-making
2005	Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products	Recommended format for obtaining race and ethnicity information for US and international clinical trials to be submitted for regulatory review to the FDA
2005	Guidance for Industry: Clinical Lactation Studies: Study Design, Data Analysis and Recommendations for Labeling	Provides recommendations for how and when to conduct clinical lactation studies and how to assess the influence of drugs or biologic products on lactation in order to assist in rational therapeutics for lactating patients
2009	Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements – Draft 2006	This guidance is intended to assist applicants in complying with the new content and format requirements of labeling for human prescription drugs and biological products

PD: Pharmacodynamics; PK: Pharmacokinetics.
Data taken from [120].

baseline QT interval values, normal ranges and appropriate heart rate correction formulae for QT intervals. These measurements can be standardized for sex and other demographic variables. Through the partnership with CSRC, tools will be developed to detect electrical cardiac safety signals specific to key subgroup populations, such as women, and assist with the understanding of cardiac safety profiles of new drugs in these populations [129].

Another initiative through the CPI that would enable efficient quantification of women's participation in clinical trials and help understand adverse outcomes in women and other subgroup populations is the FDA's data standardization initiative [131,132]. The FDA arguably holds the largest clinical trial data repository in the world. These data are a rich source of information to assess trends and signals of safety outcomes. However, the lack of universal standards for data collection and regulatory submission make this assessment a daunting task, creating a bottleneck for data collation, combination, pooling, analyses and interpretation across studies. Through the CPI's data standardization initiative, clinical trial data submitted to the FDA are being harmonized for consistency by adopting the standards from the Clinical Data Interchange Consortium [133]. In addition, pilot studies are currently ongoing where electronic legacy data residing within the FDA are being converted to the Clinical Data Interchange Consortium format for some drugs, biologics and medical devices [134]. The pooled data sets in standardized formats will enable efficient queries of women's participation in clinical trials and enable assessment of sex differences in the safety and efficacy outcomes of drug products – a task that could otherwise be overwhelming if each dataset from clinical trials were to be analyzed separately.

FDA Amendments Act: REMS & Sentinel Initiative

In 2007 the US Congress passed the FDA Amendments Act (FDAAA) that gave the FDA new authorities on postmarketing safety regulations, thus allowing the FDA for the first time to require companies to conduct additional postmarketing studies and clinical trials to improve the understanding of drug product safety [135]. Under the FDAAA authorization, the FDA can enforce safety-related labeling changes and require sponsors to comply with risk evaluation and mitigation strategies (REMS) when safety information is deemed critical for general public use of a drug [32,33]. REMS include elements to ensure safe use for those who prescribe, dispense or use the drug [136,137]. As an example, REMS is implemented for safe use of thalidomide, which is currently approved for the treatment of multiple myeloma and erythema nodosum leprosum. To prevent thalidomide's risk to pregnant women through fetal exposure and adverse outcomes, extensive information is provided on the serious risks and safe use conditions for prescribers, patients and pharmacists through REMS [138]. Through the implementation of REMS, it is anticipated that adverse drug responses (e.g., fetal exposure to thalidomide and the resulting birth defects) will be minimized.

Under FDAAA, the FDA was mandated to establish a system for postmarket safety risk identification and analysis using automated healthcare data (e.g., administrative claims databases, electronic health record system data) to monitor drug safety [135,139]. This mandate could provide a scientific framework for characterizing subgroup patient populations, such as women, who may be at increased risk for certain adverse outcomes and help to define strategies for risk mitigation and prevention. In response to this Congressional mandate, the FDA launched the Sentinel Initiative in 2008, with a goal to build and implement a national electronic system for monitoring medical product safety through the use of existing healthcare data [140]. The Sentinel Initiative released a progress report in July 2010 detailing achievements in establishing a system for monitoring the safety of medical products through the 'Mini-Sentinel' pilot project. Mini-Sentinel will initially focus on evaluating safety issues that emerge from information accessible to the FDA through medical product-development programs or early adverse event reports submitted to the FDA databases [141–143]. This effort will provide access to multiple sources of healthcare data for assessment of sex differences in the safety of the FDA-regulated products through their life cycle of use.

Requirements on content & format of labeling for human prescription drug & biological products: final rule

In recent years, there has been an increase in the length, detail and complexity of prescription drug labeling, making it harder for healthcare practitioners to find specific information and to discern the most critical information from labeling to address these challenges. In January 2006, the FDA published the final rule that amended the requirements for the content and format of labeling for human prescription drug and biological products [144].

Changes to the labeling format included the addition of introductory prescribing information titled *Highlights of Prescribing Information* (Highlights) and a *Table of Contents* (Contents) for the full prescribing information. The Highlights section of the labeling now contains selected information from the full prescribing information that healthcare practitioners most commonly reference and consider most important. These include Product Names, Boxed Warning, Recent Major Changes, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions and Use in Specific Populations. The final rule also reordered certain sections to make it easier for healthcare practitioners to access, read and use information from drug labeling. The goal of these revisions was to enhance the safe and effective use of prescription drug products and to reduce the number of adverse reactions resulting from preventable medication errors due to misunderstood or incorrectly applied drug information [145,146].

The FDA published guidances on how to implement the new labeling requirements, as well as specific guidances on selected sections of the labeling [145]. The guidances specify, for instance, that the Warning and Precautions sections should contain a discussion of risk factors for adverse reactions, such as age, sex, race, comorbid conditions, dose, duration of use and coadministered drugs. The Contraindications section should list known risk factors, such as age, sex, race and genetic vulnerability (only if it is a contraindication to drug use) [147]. The Adverse Reactions section of labeling must include a commentary on adverse reactions with clinically important information about observed differences or lack of observed differences in adverse reactions in various demographic groups (e.g., age, racial and sex) [148]. Information under the Dosage and Administration heading must contain a concise summary of the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, if any, and other clinically significant clinical pharmacology information that affects dosing recommendations [149,150]. Information regarding PK, PD or clinical trial outcomes for demographic subgroups such as age, race and sex are described in the clinical pharmacology and clinical sections of the full prescribing section of the label [151,152].

These labeling specifications regarding subgroup populations have brought to the forefront the importance of demographic considerations such as patient sex for optimizing the safety and efficacy of prescription drugs. The following examples illustrate how drug exposure and safety concerns in women are reported in the various sections of product labeling.

- Thalidomide (Thalomid®) is indicated for the acute treatment of the cutaneous manifestations of moderate-to-severe erythema nodosum leprosum. The labeling provides extensive details of potential birth defects from fetal exposure to thalidomide. As an example, the labeling includes the following information for use in women [153]: *Boxed Warning: Severe, life-threatening human birth defects. If thalidomide is*

taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug.

- Bicalutamide (Casodex®) is an androgen receptor inhibitor indicated for use in combination therapy with a luteinizing hormone-releasing hormone analog for the treatment of stage D2 metastatic carcinoma of the prostate. Labeling includes the following information for use in women and pregnancy [154]: *Contraindications: Women: Casodex has no indication for women and should not be used in this population. Pregnancy: Casodex may cause fetal harm when administered to a pregnant woman. Casodex is contraindicated in women, including those who are or may become pregnant. There are no studies in pregnant women using Casodex. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.*
- Avandia® (rosiglitazone) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. The higher fracture risk for women taking rosiglitazone is reported under the Adverse Reactions and Warnings & Precautions sections and states the following [113]: *In ADOPT, fractures were reported in a greater number of women treated with AVANDIA (9.3%, 2.7/100 patient-years) compared with glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand and foot.* (See Warnings and Precautions [5.7]). *The observed incidence of fractures for male patients was similar among the 3 treatment groups.*

Conclusion

The drug-development enterprise and the regulatory review and approval processes have experienced considerable advancements since the 1980s and increased interest in interindividual response differences and development of the FDA regulations and guidances to understand these differences are just some of the milestones of this era. Heightened attention to variable patient outcomes has guided the healthcare community to consider demographic factors in optimizing treatment. Understanding and effectively communicating varied patient

Key issues

- Historical events such as fetal exposure to thalidomide and subsequent adverse outcomes led to the unintended exclusion or inadequate representation of women in clinical drug trials.
- A setback in the biological understanding of the role that sex differences play in disease prevalence, drug treatment needs and health outcomes led to public outcry and a societal impetus for more focus on studying both men and women in clinical drug trials.
- Emerging examples of sex differences in adverse outcomes further reinforced the need to study and understand the underlying mechanisms responsible for sex differences in health outcomes.
- The US FDA's regulations and guidances emphasized the importance of studying demographic variables such as age, sex and racial subgroup factors during drug product development.
- Through a landmark Critical Path Initiative (CPI), the FDA leveraged partnerships with industry, academia, regulators, patient advocacy groups and healthcare providers to improve the FDA's scientific and bioinformatics infrastructure, apply advanced tools such as genomics, proteomics and imaging techniques to modernize trial designs and data analysis approaches to understand at-risk populations, and to advance individualized therapeutics.
- Select CPI programs that have advanced the sciences necessary to understand sex-specific drug responses include the electrocardiogram (ECG) warehouse and the data standardization initiative. Through the ECG warehouse collaboration, key subgroup populations at risk of drug-induced cardiac safety will be identified. Through the data standardization initiative, electronic data submission to the FDA will be harmonized and will enable efficient queries of subgroup participation in clinical trials and their adverse outcomes.
- Public scrutiny of safety issues related to medical products imposed new Congressional mandates for the FDA. Closer scrutiny on assessing the safety of therapeutics, both premarket and postmarket, became the cornerstone of FDA Amendments Act. New authorities were granted to the FDA to require additional clinical data for safety when deemed important and to communicate evidence-based safety information to patients and healthcare providers. Additionally FDA established an active postmarket surveillance system, the Sentinel Initiative, to continue the gathering of safety data of products using available electronic health records and to continually update the safety of FDA-regulated products.
- A new format for prescription drug labels was created to enable easy access to the most important information regarding product efficacy and safety. Under this initiative, safety-related outcomes are listed prominently for specific vulnerable populations. Relevant information on safety is communicated through labeling sections such as Boxed Warnings, Contraindications, Warnings, Precautions and Adverse Effects. Key information is provided as the Highlights of full prescribing information of product label. The new format allows the most up-to-date critical information to be available to patients and healthcare professionals in an easy-to-read format with the ultimate goal of protecting public health.
- The drug-development enterprise and regulatory review and approval processes undergo close ongoing scrutiny by regulatory bodies, the public, US Congress and academic and private organizations. Through adopting novel approaches, modernizing the review and approval systems and enhancing communication of the most up-to-date information on safety and efficacy of its regulated products, the FDA ensures continual refinement of its regulatory policies and practices to fulfill its public health mission.

responses to minimize risk are challenges that rely on a commitment from multiple stakeholders. Through new programs and legislative mandates, the FDA has leveraged its resources to build partnerships with patient groups, healthcare professionals, academia and investigators to further the science of individualized therapy. These approaches assimilate information throughout a product's life cycle, integrating premarket and postmarket experiences to understand drug safety in subgroup populations. These initiatives should identify patient populations at increased risk and to develop strategies for preventable harm from use of prescription drugs in such populations. Improving benefit versus risk profiles of the FDA-regulated products is, after all, the mainstay of the FDA's mission for public health.

Expert commentary & five-year view

Despite the robustness of the premarket drug development and the regulatory review and approval processes, new information is continually and inevitably gleaned from the postmarket experience due to an expanded duration and patient use. While the FDA relies on an active involvement of all healthcare stakeholders to improve its understanding of drug safety, the public depends on the FDA to communicate the most up-to-date information so that the most informed treatment decisions are made.

The FDA has launched several recent initiatives to standardize, capture, process and disseminate clinical information and subsequently optimize the use of drug products. The intent of these initiatives is to address the dilemma of capturing safety and efficacy information through a product life cycle approach and to share the information in a timely fashion with patients and healthcare providers. Combining existing pharmacological information, individual patients' mechanistic knowledge through novel technologies such as genomics and imaging tools, and population-based data on treatment outcomes gathered from electronic medical records should collectively enable better predictions of drug-related adverse responses. Using the impetus provided by Congress through the passage of the FDAAA, the FDA is strengthening its safety infrastructure and leveraging its resources to partner with stakeholders to further the understanding of safety outcomes in specific at-risk patient populations.

The FDA's investment in the new approaches discussed in this paper will advance the understanding of interindividual response differences, provide for a better understanding of sex-based treatment outcomes and present opportunities to minimize preventable harm from drug use.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Adam E, Decker DG, Herbst AL *et al.* Vaginal and cervical cancers and other abnormalities associated with exposure in utero to diethylstilbestrol and related synthetic hormones. *Cancer Res.* 37(4), 1249–1251 (1977).

2 Seminar on women in clinical trials of FDA-regulated products: who participates and who decides? *Food Drug Law J.* 48, 61–226 (1993).

3 Department of Health and Human Services. Women's Health: Report of the Public Health Service Task Force on Women's Health Issues. Public Health Report, DHHS Publication no. 85–50206. DHHS, DC, USA (1985).

4 Merkatz R, White-Junod S. Historical background of changes in FDA policy on the study and evaluation of drugs in women. *Acad. Med.* 69(9), 703–707 (1994).

5 Pinn V. The role of NIH office of research on women's health. *Acad. Med.* 69(9), 698–702 (1994).

6 McCarthy C. Historical background of clinical trials involving women and minorities. *Acad. Med.* 69(9), 695–698 (1994).

7 Gandhi M, Aweeka F, Greenblatt RM *et al.* Sex differences in pharmacokinetics and pharmacodynamics. *Annu. Rev. Pharmacol. Toxicol.* 44, 499–523 (2004).

8 Schwartz JB. The current state of the knowledge on age, sex and their interactions on clinical pharmacology. *Clin. Pharmacol. Ther.* 82(1), 87–89 (2007).

9 Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin. Pharmacokinet.* 48(3), 114–157 (2009).

10 Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? pharmacogenetics, pharmacokinetics, and pharmacodynamics. *J. Women's Health* 14(1), 19–29 (2005).

11 Huang SM, Miller M, Toigo T *et al.* Evaluation of drugs in women. In: *Principles of Gender Specific Medicine (Volume 2).* Lagato MJ (Ed.). Elsevier Academic Press, Oxford, UK, 848–859 (2007).

12 Jann MW, ZumBrunnen TL, Tenjarla SN *et al.* Relative bioavailability of ondansetron 8-mg oral tablets versus two extemporaneous 16-mg suppositories: formulation and gender differences. *Pharmacotherapy* 18(2), 288–294 (1998).

13 Drici MD, Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Saf.* 24(8), 575–585 (2001).

14 Roukoz H, Saliba W,. Dofetilide: a new class III antiarrhythmic agent. *Expert Rev. Cardiovasc. Ther.* 5(1), 9–19 (2007).

15 Salazar D, Much D, Nichola P *et al.* A pharmacokinetic-pharmacodynamic model of d-sotalol Q-Tc prolongation during intravenous administration to healthy subjects. *J. Clin. Pharmacol.* 37, 799–809 (1997).

16 Waldo A, Camm AJ, deRuyter H *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 348, 7–12 (1996).

17 Benton R, Sale M, Flockhart D *et al.* Greater quinidine-induced QTc interval prolongation in women. *Clin. Pharmacol. Ther.* 67(4), 413–418 (2000).

18 Drici M, Burklow T, Haridasse V *et al.* Sex hormones prolong the QT interval and downregulate potassium channel

expression in the rabbit heart. *Circulation* 94, 1471–1474 (1996).

19 Rodriguez I, Kilborn MJ, Liu X *et al.* Drug-induced QT prolongation in women during the menstrual cycle. *JAMA* 285(10), 1322–1326 (2001).

20 Rautaharju P, Zhou S, Wong S *et al.* Sex differences in the evolution of electrocardiographic QT interval with age. *Can. J. Cardiol.* 8, 690–695 (1992).

21 Alexander K, Chen A, Roe M *et al.* Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 294(24), 3108–3116 (2005).

22 Campbell N, Hull R, Brant R *et al.* Different effects of heparin in males and females. *Clin. Invest. Med.* l21(2), 71–78 (1998).

23 Cho L, Topol E, Balog C *et al.* Clinical benefit of glycoprotein Iib/IIIa blockade with abciximab is independent of gender. Pooled analysis from EPIC, EPILOG and EPISTENT Trials. *J. Am. Coll. Cardiol.* 36(2), 381–386 (2000).

24 Kernan WN, Viscoli CM, Brass LM *et al.* Phenylpropanolamine and the risk of hemorrhagic stroke. *N. Engl. J. Med.* 343(25), 1826–1832 (2000).

25 Kahn SE, Zinman B, Lachin JM, et.al. Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in Type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 31(5), 845–851 (2008).

26 Meymeh RH, Wooltorton E. Health and drug alerts: diabetes drug pioglitazone (Actos): risk of fracture. *CMAJ* 177 (7) 723–724 (2007).

27 Temple R. Development of drug law, regulations, and guidance in the United States. In: *Principles of Pharmacology. Basic Concepts and Clinical Applications*. Munson PL (Ed.). Chapman & Hall, International Thompson Publishing, NY, USA, 1643–1664 (1998).

28 Yang Y, Carlin A, Faustino P *et al.* Participation of women in clinical trials for new drugs approved by the Food and Drug Administration in 2000–2002. *J. Women's Health* 18(3), 303–310 (2009).

29 Pinnow E, Sharma P, Parekh A *et al.* Increasing participation of women in early phase clinical trials approved by the FDA. *Women's Health Issues* 19, 89–93 (2009).

30 Woodcock J, Woosley R. The FDA critical path initiative and its influence on new drug development. *Ann. Rev. Med.* 59, 1–12 (2008).

31 Parekh A, Sanhai W, Marts S *et al.* Advancing women's health via FDA critical path initiative. *Drug Discov. Today Technol.* 4(2), 69–73 (2007).

32 Seligman P, Osborne SF. Perspectives on early communication of drug risk to the public. *Clin. Pharmacol. Ther.* 85(3), 335–333 (2009).

33 Honig P. Drug safety and the role of clinical pharmacology in the safe use of therapeutics. *Clin. Pharmacol. Ther.* 85(3), 225–228 (2009).

Websites

101 UNSW embryology. Abnormal development – thalidomide http://embryology.med.unsw.edu.au/Defect/page5i.htm (Accessed 9 November 2010)

102 A crime against women: AH Robins and the Dalkon Shield http://multinationalmonitor.org/hyper/issues/1986/0115/index.html (Accessed 9 November 2010)

103 FDA Gender Guideline (1977). General Considerations for the Clinical Evaluation of Drugs. (HEW Publication No. FDA 77–3040) www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071682.pdf (Accessed 9 November 2010)

104 Redmond CK, Buring JE. Recruitment and retention of women in clinical studies. Design and implementation issues in clinical studies. NIH Publication 95–3756 http://orwh.od.nih.gov/pubs/Women_in_Clinical_Studies.pdf (Accessed 20 December 2010)

105 Zofran® (ondansetron) US FDA Drug Product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=43921 (Accessed 29 June 2011)

106 Zyprexa® (olanzapine) US FDA drug product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=31419 (Accessed 9 November 2010)

107 Tikosyn (dofetilide) US FDA drug product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=46801 (Accessed 29 June 2011)

108 Betapace (sotalol) US FDA drug product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=33684 (Accessed 9 November 2010)

109 Quinidine sulfate (quinidine) US FDA drug product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9391 (Accessed 20 December 2010)

110 US General Accounting Report. Drug safety: most drugs withdrawn in recent years had greater health risks for women http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=38753 (Accessed 29 June 2011)

111 FDA CDER nonprescription drugs advisory committee meeting on safety issues of phenylpropanolamine (PPA) in over-the-counter drug products. Thursday October 19, 2000 www.fda.gov/ohrms/dockets/ac/00/transcripts/3647t1a.pdf (Accessed 9 November 2010)

112 FDA issues public health warning on phenylpropanolamine www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm150763.htm (Accessed 9 November 2010)

113 Avandia (rosiglitazone) US FDA product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=38243 (Accessed 9 November 2010)

114 Actos (pioglitazone) US FDA product labeling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=22567 (Accessed 29 June 2011)

115 FDA Overview: Kefauver–Harris Amendment of 1962 www.emedicinehealth.com/fda_overview/article_em.htm (Accessed 17 December 2010)

116 Evaluation of gender differences in clinical investigations. Information sheet: FDA guidance for institutional review boards and clinical investigators http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=38243 (Accessed 29 June 2011)

117 FDA Guidance for Industry. Gender Guideline 1993. Study and evaluation of gender differences in clinical trials www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072044.pdf (Accessed 20 December 2010)

118 US Department of Health and Human Services, FDA. Investigational new drug

applications; Amendment to clinical hold regulations for products intended for life-threatening diseases and conditions. *Fed. Register* 65, 34963–34971 (2000) www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120264.htm (Accessed 9 November 2010)

119 Specific requirements on content and format of labeling for human prescription drug and biological products described in Sec. 201.57.; 201.56(b)(1) www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57 (Accessed 21 November 2010)

120 FDA Guidances (Drugs) www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (Accessed 21 November 2010)

121 US General Accounting Office. Women's Health: FDA needs to ensure more study of gender differences in prescription drug testing. HRD-93–17. 29, 1–39 (1992) http://archive.gao.gov/d35t11/147861.pdf (Accessed 9 November 2010)

122 US General Accounting Office. Women's Health: Women sufficiently represented in new drug testing, but FDA oversight needs improvement. 2001, 1–36 (2001) www.gao.gov/new.items/d01754.pdf (Accessed 9 November 2010)

123 Evelyn B, Toigo, T, Banks D *et al.* Women's participation in clinical trials and gender-related labeling: a review of new molecular entities approved 1995–1999 www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/Participatinginclinicaltrials/ucm197788.htm (Accessed 9 November 2010)

124 Woodcock J, Behrman R, Dal Pan G. Role of postmarketing surveillance in contemporary medicine. *Annual Review of Medicine.* August 2010 www.annualreviews.org/doi/full/10.1146/annurev-med-060309-164311 (Accessed 29 June 2011)

125 Critical path: challenges and opportunities report. March 2004 www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm#execsummary (Accessed 20 December 2010)

126 US FDA Critical Path Initiative www.fda.gov/oc/initiatives/criticalpath/whitepaper.html (Accessed 9 November 2010)

127 US FDA Existing Public Private Partnerships www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm166082.htm#CSRC (Accessed 9 November 2010)

128 Cardiac Safety Research Consortium (CSRC) www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm231121.htm (Accessed 20 December 2010)

129 FDA and Duke Clinical Research Institute form partnership to collaborate on cardiac safety virtual 'warehouse' of electrocardiograms will serve as primary tool in cutting-edge safety research www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108744.htm (Accessed 9 November 2010)

130 Guidance for Industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf (Accessed 9 November 2010)

131 Slides for the November 15 2010 Meeting of the Science Board to the FDA www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/ucm233252.htm (Accessed 20 January 2011)

132 CDER Data Standards Plan Version 1.0 – Draft www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM214120.pdf (Accessed 18 November 2010)

133 Written notice of participation by the Clinical Data Interchange Standards Consortium (CDISC) and written statement for discussion topics to be addressed in the FDA Public Hearing: electronic submission of regulatory information, and creating an electronic platform for enhanced information management www.fda.gov/ohrms/dockets/dockets/06n0464/06N-0464-EC10-Attach-1.pdf (Accessed 9 November 2010)

134 PDUFA information technology plans www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm183308.htm (Accessed 18 November 2010)

135 Full Text of FDAAA Law www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstothe FDCAct/FoodandDrugAdministration AmendmentsActof2007/FullTextofFDAAALaw/default.htm (Accessed 9 November 2010)

136 Guidance for industry format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM184128.pdf (Accessed 9 November 2010)

137 US FDA Approved Risk Evaluation and Mitigation Strategies (REMS) www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationfor PatientsandProviders/ucm111350.htm (Accessed 9 November 2010)

138 REMS: System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafety InformationforPatientsandProviders/UCM222649.pdf (Accessed 21 November 2010)

139 Postmarket drug safety information for patients and providers www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationfor PatientsandProviders/default.htm (Accessed 9 November 2010)

140 FDA's Sentinel Initiative: background www.fda.gov/Safety/FDAsSentinel Initiative/ucm149340.htm (Accessed 9 November 2010)

141 The Sentinel Initiative; progress report, November 2010 www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf (Accessed 9 November 2010)

142 FDA awards contract to Harvard Pilgrim to develop pilot for safety monitoring system www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm196968.htm (Accessed 18 November 2010)

143 FDA information systems. Sentinel Initiative seek more timely drug safety information http://formularyjournal.modernmedicine.com/formulary/Modern+Medicine+Feature+Articles/FDA-information-systems-Sentinel-Initiative-seek-m/ArticleStandard/Article/detail/664515 (Accessed 18 November 2010)

144 FDA announces the final rule on the requirements for prescribing information for drug and biological products, January 18 2006: summary www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm085169.htm (Accessed 9 November 2010)

145 FR notice: Department of Health and Human Services, Food and Drug Administration, docket no. 2005D-0011, draft guidances for industry on the content and format of labeling for human prescription drug and biological products; availability www.fda.gov/OHRMS/DOCKETS/98fr/06-543.pdf (Accessed 20 December 2010)

146 FDA announces new prescription drug information format to improve patient safety www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108579.htm (Accessed 9 November 2010)

147 Guidance for industry: warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products – content and format www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf (Accessed 20 December 2010)

148 Adverse reactions section of labeling for human prescription drug and biological products — content and format www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf (Accessed 20 December 2010)

149 Guidance for industry: labeling for human prescription drug and biological products — implementing the new content and format requirements www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf (Accessed 20 December 2010)

150 Guidance for industry: dosage and administration section of labeling for human prescription drug and biological products – content and format www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075066.pdf (Accessed 20 December 2010)

151 Guidance for industry: clinical studies section of labeling for human prescription drug and biological products – content and format www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075059.pdf (Accessed 20 December 2010)

152 Guidance for industry: clinical pharmacology section of labeling for human prescription drug and biological products: content and format (draft) www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf (Accessed 20 December 2010)

153 Thalomid (thalidomide) capsule US FDA product labelling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=43637&CFID=57319287&CFTOKEN=e2a3d40364d27995-A2BEDBCC-B9D0-BED7-98068B0157DA206A&jsessionid=ca30169d87b9f474f453 (Accessed 29 June 2011)

154 Casodex® (bicalutamide) tablet US FDA product labelling http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=23990#section-5 (Accessed 20 December 2010)