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United States General Accounting Office
Washington, DC 20548

January 19, 2001

The Honorable Tom Harkin
The Honorable Olympia J. Snowe
The Honorable Barbara A. Mikulski
United States Senate

The Honorable Henry A. Waxman
House of Representatives

Subject: Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women

The Food and Drug Administration (FDA) approves drugs for sale in the United States based on its determination that the clinical benefits of a drug outweigh its potential health risks. To make this decision, FDA reviews supporting data collected from several thousand patients during the drug's development. Once a drug is approved for marketing and used by potentially hundreds of thousands of patients, however, the type, rate, and severity of adverse events caused by the drug can be much different than those detected during the drug's development. In some cases, FDA or drug manufacturers have acted to remove from the market drugs that have been shown to have unacceptable health risks once they were in widespread use.

You requested that we identify drug products withdrawn from the market in the United States since January 1, 1997, and that we note which of the withdrawn drugs posed greater health risks for women than for men. We collected this information from publicly available sources, primarily FDA documents and research articles from the medical literature. We also consulted drug safety experts. We looked only at prescription pharmaceuticals, not at vaccines or over-the-counter medicines.[1] We conducted our work from December 2000 to January 2001 in accordance with generally accepted government auditing standards.

[1]Although not included in our sample of withdrawn drugs, ingredients are occasionally removed from nonprescription drugs because they are proven to pose serious health risks. For example, on Nov. 6, 2000, FDA took steps to remove phenylpropanolamine (PPA) from all drug products and requested that all drug companies discontinue marketing products containing PPA. PPA, which could be found in many over-the-counter (OTC) and prescription cough and cold medications and OTC weight loss products, was reported to increase the risk of hemorrhagic stroke (bleeding into the brain or tissue around the brain) in women but not in men. See W.N. Kernan and others, "Phenylpropanolamine and the Risk of Hemorrhagic Stroke," *New England Journal of Medicine*, Vol. 343, No. 25 (2000), pp. 1826-32.

In summary, we found that 10 prescription drugs have been withdrawn from the U.S. market since January 1, 1997. Eight of the 10 prescription drugs posed greater health risks for women than for men: four of these may have led to more adverse events in women because they were prescribed more often to women than to men, while the other four had more adverse events in women even though they were widely prescribed to both women and men. Of the two remaining withdrawn drugs, one belongs to a class of drugs known to pose a greater health risk for women, but we were unable to find direct evidence that the adverse events that contributed to its withdrawal occurred predominantly in women. We found no direct evidence that the health risks for the remaining withdrawn drug differed for women and men. In comments on a draft of this letter, FDA generally agreed with our analysis.

Eight of the 10 prescription drugs withdrawn since January 1, 1997, posed greater health risks for women than for men (see table 1). For four of the withdrawn drugs, the greater health risk may have been due to a higher level of use among women. For example, the appetite suppressants Pondimin and Redux were withdrawn from the U.S. market because they caused valvular heart disease in some patients. Although the majority of the reported cases were in women, most of the users were women, so the apparent gender-related effects could be a reflection of the products' usage patterns.[2] Similarly, women accounted for more than two-thirds of the deaths due to liver failure in patients taking Rezulin, but women also were prescribed Rezulin more often than men.[3] Finally, it is likely that Lotronex posed a greater health risk for women because the drug was approved to treat irritable bowel syndrome in women only.[4]

Four other withdrawn drugs posed greater health risks for women even though they were widely prescribed to both women and men. Posicor, which was approved for the treatment of hypertension and angina, slowed or stopped the heart rate in otherwise healthy people, especially elderly women, and interacted with 26 different drugs.[5] Greater health risks for women may be due to physiological differences that

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[2]See FDA, Center for Drug Evaluation and Research (CDER), *Questions and Answers About the Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux)*, http://www.fda.gov/cder/news/phen/fenphenqa2.htm (downloaded Dec. 20, 2000); H.M. Connolly and others, "Valvular Heart Disease Associated with Fenfluramine-Phentermine,"*New England Journal of Medicine*, Vol. 337, No. 9 (1997), pp. 581-88; D.J. Graham, and L. Green, "Further Cases of Valvular Heart Disease Associated with Fenfluramine-Phentermine,"*New England Journal of Medicine,* Vol. 337, No. 9 (1997), p. 635.

[3]See J. Kohlroser and others, "Hepatotoxicity Due to Troglitazone: Report of Two Cases and Review of Adverse Events Reported to the United States Food and Drug Administration," *American Journal of Gastroenterology,* Vol. 95, No. 1 (2000), pp. 272-76; FDA, CDER, presentation of D. Graham, Endocrinologic and Metabolic Drugs Advisory Committee Meeting No. 72 (Mar. 26, 1999), pp. 94-95.

[4]See FDA talk paper, *Glaxo Wellcome Decides to Withdraw Lotronex From the Market* (Nov. 28, 2000), http://www.fda.gov/bbs/topics/answers/anhs01058.html (downloaded Dec. 20, 2000); FDA, CDER, *Lotronex Questions and Answers,* http://www.fda.gov/cder/drug/infopage/lotronex/lotronex-qa.htm (downloaded Dec. 20, 2000).

[5]See Medwatch: The FDA Medical Products Reporting Program, *Background: Posicor Labeling Changes* (Dec. 18, 1997), http://pharminfo.com/medwatch/mwrpt31.html (downloaded Nov. 29, 2000).

Table 1: Prescription Drugs Withdrawn From the United States Market, Jan. 1, 1997 Through Dec. 31, 2000

Drug	Type of Drug	Date Approved	Date Withdrawn	Primary Health Risk
Prescription Drugs With Evidence of Greater Health Risks in Women				
Pondimin (fenfluramine hydrochloride)	Appetite suppressant	6/14/1973	9/15/1997	Valvular heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant	4/29/1996	9/15/1997	Valvular heart disease
Seldane[a] (terfenadine)	Antihistamine	5/8/1985	2/27/1998	Torsades de Pointes (potentially fatal irregular heartbeat)
Posicor (mibefradil dihydrochloride)	Cardiovascular	6/20/1997	6/8/1998	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal (astemizole)	Antihistamine	12/19/1988	6/18/1999	Torsades de Pointes
Rezulin (troglitazone)	Diabetic	1/29/1997	3/21/2000	Liver failure
Propulsid[b] (cisapride monohydrate)	Gastrointestinal	7/29/1993	7/14/2000	Torsades de Pointes
Lotronex (alosetron hydrochloride)	Gastrointestinal	2/9/2000	11/28/2000	Ischemic colitis (intestinal inflammation due to lack of blood flow)
Prescription Drugs Without Evidence of Greater Health Risks in Women				
Raxar (grepafloxacin hydrochloride)	Antibiotic	11/6/1997	11/1/1999	Torsades de Pointes
Duract (bromfenac sodium)	Analgesic and anesthetic	7/15/1997	6/22/1998	Liver failure

[a]Seldane-D was also withdrawn from the market Feb. 27, 1998. Terfenadine was the active ingredient in both Seldane and Seldane-D; Seldane-D also contained the decongestant pseudoephedrine.

[b]Propulsid remains minimally available on a patient-by-patient basis for those with severely debilitating conditions.

Source: GAO analysis.

make women differentially more susceptible to some drug-related health risks. Seldane, Hismanal, and Propulsid can in some circumstances prolong the interval between the heart muscle's contractions and induce Torsades de Pointes (TdP), a potentially fatal cardiac arrhythmia. Women have a higher incremental risk of suffering an arrhythmia after taking these drugs than do men probably because (1) the interval between heart muscle contractions is naturally longer for women than for men and (2) male sex hormones moderate the heart muscle's sensitivity to these drugs.[6]

The remaining two withdrawn drugs have not demonstrated a greater health risk for women. The first, Raxar, belongs to a class of drugs (fluoroquinolone antibiotics) known to pose a greater health risk for women. Since the early 1990s, there has been mounting evidence that fluoroquinolone antibiotics, antiarrhythmic drugs, antihistamines (for example, Seldane and Hismanal), and gastrointestinal prokinetics (for example, Propulsid) prolong heart muscle contractions and induce TdP.[7] However, there is no conclusive evidence that the adverse events that contributed to Raxar's withdrawal occurred primarily in women. For the second, Duract, we found no evidence that the risk of adverse events differed for women and men.

It is important to note that an examination of drug withdrawals, by itself, does not provide a complete picture of drug safety. First, drug withdrawals do not reflect a judgment concerning the absolute safety of a drug but reflect a judgment about the risks and rewards of a drug in the context of alternative treatments. For instance, despite the documented deaths from liver failure among patients taking Rezulin, the drug was not withdrawn from the market until FDA approved new, safer medications with similar benefits. On the other hand, Raxar was withdrawn from the market on the basis of relatively few adverse event reports because alternative treatments were readily available.

Second, drug withdrawals may occur because the drugs are used incorrectly by health professionals and patients, not because the drugs are inherently dangerous

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[6]See Georgetown Center for Education and Research on Therapeutics, *Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes* (Sept. 1, 2000), http://www.torsades.org (downloaded Dec. 20, 2000); R.L. Woosley, "From Bench to Bedside: Role of Gender-Based Therapeutics in the Clinical Care of Women," *Journal of Women's Health,* Vol. 7, No. 1 (1998), pp. 21-23; S.N. Ebert and others, "Female Gender as a Risk Factor for Drug-Induced Cardiac Arrhythmias: Evaluation of Clinical and Experimental Evidence," *Journal of Women's Health,* Vol. 7, No. 5 (1998), pp. 547-57; C. Hart, "Monitoring Medications in the Marketplace," *Modern Drug Discovery,* Vol. 3, No. 5 (2000), pp. 40-41, 43-44, http://pubs.acs.org/hotartcl/mdd/oo/jun/mddhart.html (downloaded Dec. 18, 2000); W. Haverkamp, "The Potential for QT Prolongation and Proarrhythmia by Non-Antiarrhythmic Drugs: Clinical and Regulatory Implications," Report on a Policy Conference of the European Society of Cardiology 2000, *European Heart Journal,* http://www.idealibrary.com (downloaded Dec. 12, 2000); J.T. Barbey and others, "Spontaneous Adverse Event Reports of Serious Ventricular Arrhythmias, QT Prolongation, Syncope, and Sudden Death in Patients Treated with Cisapride" (obtained from J.T. Barbey Jan. 5, 2000, submitted for publication).

[7]See Woosley, pp. 21-23; Ebert and others, pp. 547-57; Hart, pp. 40-41, 43-44; L. Patmore and others, "Effects of Sparfloxacin, Grepafloxacin, Moxifloxacin, and Ciprofloxacin on Cardiac Action Potential Duration," *European Journal of Pharmacology,* Vol. 406, No. 3 (2000), pp. 449-52.

when used correctly. For example, Duract was approved by FDA only for short-term use (less than 10 days) for acute pain, but some physicians continued to prescribe it for longer periods despite efforts by FDA and the manufacturer to educate physicians about the dangers of doing so. Similarly, the health risks associated with Seldane occurred when the drug was taken in combination with medications that were contraindicated on Seldane's label.

Third, the off-label use of drugs also can be problematic because such use may not have been shown to be safe and effective. For example, while Pondimin (fenfluramine) was approved for short-term use as an appetite suppressant, it was increasingly prescribed and used in combination with the appetite suppressant phentermine as a part of a long-term weight loss and management program. The off-label use of this combination known as "fen-phen" posed serious health risks for women.[8]

AGENCY COMMENTS

We received written comments from FDA on a draft of this letter (see enclosure). FDA generally agreed with our description of the issues and provided technical comments, which we have incorporated where appropriate. FDA also suggested that we distinguish more clearly between withdrawn drugs that led to more adverse events in women because they were prescribed more often to women and those that caused more adverse events in women even though the drugs were roughly prescribed on an equal basis to women and men. We have revised the letter to clarify this distinction. FDA also suggested that we include Raxar in the list of drugs with greater health risks for women because it belongs to a class of drugs with known risks for women. We did not do so because, as FDA's comments acknowledge, it has not been shown that the adverse events that led to Raxar's withdrawal occurred primarily in women.

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[8]The use of phentermine alone has not been associated with valvular heart disease.

We plan no further distribution of this correspondence until 30 days after the date of this letter. At that time, we will send copies of this letter to the Commissioner of FDA and to others who request it. The letter will also be available on GAO's home page at http://www.gao.gov.

Major contributors to this letter were Martin T. Gahart, Emily J. Rowe, and Lisanne Bradley. Please contact me at (202) 512-7119 if you have any questions.

Janet Heinrich, Director
Health Care—Public Health Issues

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 18 2001

Ms. Janet Heinrich
Director, Health Care - Public Health Issues
United States General Accounting Office
441 G Street, Northwest, Room 5A14
Washington, D.C. 20548

Dear Ms. Heinrich:

Please find the enclosed comments from the Food and Drug Administration on the General Accounting Office (GAO) draft report entitled, Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women (GAO-01-286R).

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosure

FOOD AND DRUG ADMINISTRATION COMMENTS ON THE GENERAL ACCOUNTING OFFICE DRAFT REPORT ENTITLED, "DRUG SAFETY: Most Drugs Withdrawn in recent Years Had Greater Health Risks for Women" GAO 01-286R

The Food and Drug Administration (FDA) appreciates the opportunity to review the draft and provide comments for your consideration on the report entitled, Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women," GAO 01-286R. FDA has general as well as technical comments on this draft report.

GENERAL COMMENTS:

The report is a thoughtful, fair analysis although it appears to overstate its conclusions. Our comments represent "refinements," not disagreements.

The table provides no information on how the conclusion about categorization (greater risk or not) was reached. In the text, the report acknowledges that the majority of drugs judged to be at greater risk (although we are not told how that conclusion was reached) were prescribed more often in women. This would suggest that the conclusion about greater risk was reached on the basis of finding an excess number of adverse reactions in women. In this case, the report at the very least should say, "it appears these drugs may present a greater risk for women based on the number of cases reported."

Although discussed eventually, it is suggested that the report should distinguish the cases up front. A crucial distinction should be made early between (1) drugs that cause a greater rate or severity of injury in women than men when equal numbers are treated and (2) drugs that cause more events in women because women use more of the drug (fenfluramine, alosetron). Among the drugs we know women are more susceptible to Torsade de Pointes arrhythmias than men, so that a greater rate would be expected (case 1), are Seldane, Posicor, Hismanal, Propulsid (and Raxar too, even if not shown), i.e. five of ten products. Pondimin, Redux and Lotronex are used more in women (Lotronex was only for women) i.e. (case 2). This leaves merely troglitazone as a drug with interesting or novel implications although as test notes, more users were women.

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