Are Pharmaceutical Market Withdrawals Preventable? A Preliminary Analysis

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Are Pharmaceutical Market Withdrawals Preventable? A Preliminary Analysis

Jaya Sai V. Daggumalli, BPharm, MS[1] and Irwin G. Martin, PhD[1]

Abstract

Some drugs have been removed from the market once it had been determined that their risks outweighed their benefits. Withdrawals negatively impact patients using the drugs as well the pharmaceutical companies who devoted tremendous resources to research, development, and marketing. Therefore, there is a desire to minimize drug withdrawals by learning from previous incidents. Hints of the problems that lead to eventual market withdrawal might be found in the initial New Drug Application (NDA). If inappropriate approvals could be prevented, patients' safety might be protected and withdrawals would not be necessary. Drugs withdrawn between 2001 and 2010 (n = 15) were considered for this investigation. The primary adverse events that led to the withdrawal of these 15 drugs were compared with the data available in the original NDA medical review. From the 15 drugs considered, sufficient information for analysis was available for only 7 drugs. Among the 7 drugs analyzed, the safety data found for 2 particular drugs suggested potential safety signals. Preliminary analyses suggest that the drug withdrawals could not have been predicted for the majority of drugs removed from the market.

Keywords

regulatory affairs, drug safety, marketing withdrawal, FDA, NDA

Introduction

Drug development and approval is an incredibly difficult and complex process. Unfortunately, some drugs are withdrawn from the market due to safety concerns or lack of efficacy. According to the US Food and Drug Administration (FDA) statistics published annually in the Center for Drug Evaluation and Research (CDER) reports, after the introduction of the Prescription Drug User Fee Act (PDUFA) in the early 1990s, the annual withdrawal rate of New Molecular Entities (NMEs) due to safety concerns averaged $\sim 5\%$ of approved drugs.[1]

According to the list compiled under the statutory requirements of the Food and Drug Modernization Act (FDAMA) of 1997, there were about 60 drug products that have been withdrawn or removed from the market.[2] According to the FDA's annual CDER reports, a total number of 33 drugs through 2010 have been withdrawn from the market due to safety concerns.[3] The history of approvals and safety-based withdrawal of NMEs is summarized in 5-year intervals from 1980 to 2010 in Figure 1.

In an attempt to determine if the market withdrawal of discontinued drugs could have been predicted based on the data in the original New Drug Application (NDA), data supporting the individual drug approvals were compared to the reasons for eventual market withdrawals.

Methods

Drugs withdrawn in the 10-year period of 2001-2010 were reviewed using the FDA's MedWatch website.[4] Fifteen drugs were withdrawn during this time. Table 1 lists drugs withdrawn during the study period and the reason for their withdrawal.

The events responsible for withdrawal of these 15 drugs were compared to the data available in the medical reviews for the initial NDA approvals. Medical officer reviews for each product may be found by selecting the bullet point "Approval History, Letters, Reviews, and Related Documents" on the web page for each approved drug in the database Drugs@FDA: FDA Approved Drug Products. This database may be found at www.fda.gov/drugs/default.htm by selecting "Drug Information (Drugs @FDA)" in the Spotlight column. Predictability of eventual market withdrawal was sought.

[1] School of Health Sciences, Eastern Michigan University, Ypsilanti, MI USA

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Corresponding Author:
Irwin G. Martin, PhD, School of Health Sciences, Eastern Michigan University, Ypsilanti, MI 48197, USA
Email: imartin2@emich.edu

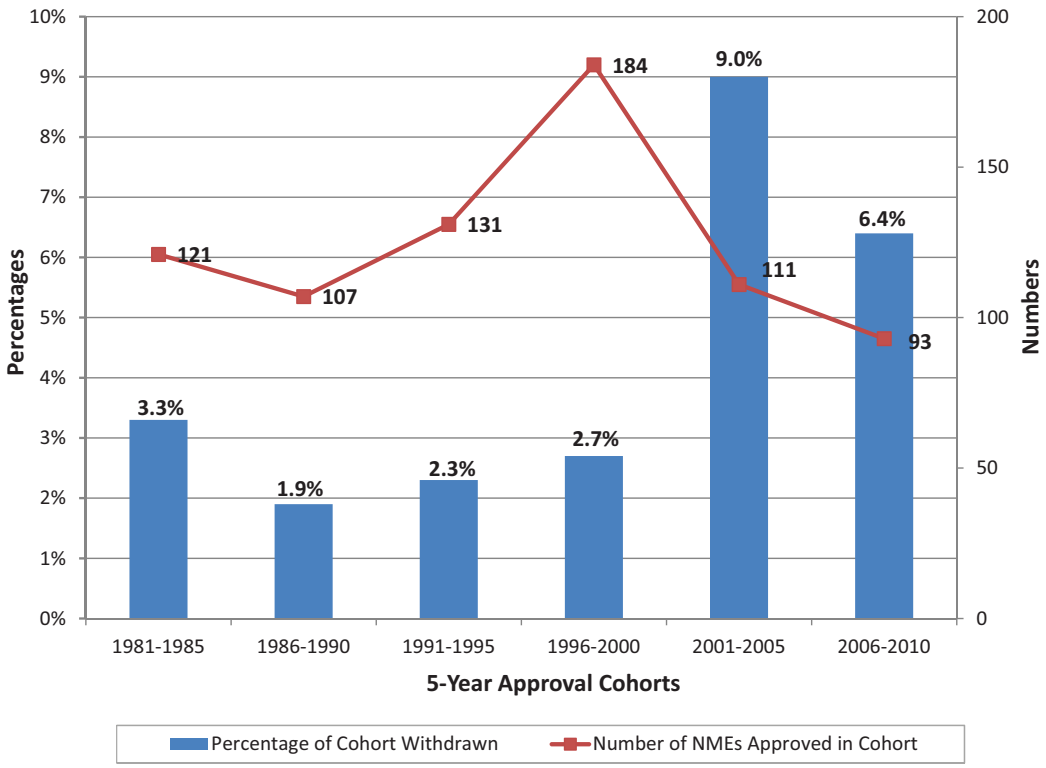

Figure 1. Safety-based NME withdrawal percentages from 1980-2010. Data are adapted from the report "Center for Drug Evaluation and Research. Report to the Nation. Improving Public Health Through Human Drugs."[1] The figure includes the number of NMEs approved in a 5-year cohorts and the percentage of the safety-based NME withdrawals in the same period. NMEs, New Molecular Entities.

Table 1. Drugs withdrawn from marketing that had been approved during the study period 2001-2010.[3]

Brand Name (Generic Name)	Reason for Withdrawal
Baycol (cerivastatin)	Rabdomylosis
Raplon (rapicuronium)	Bronchospasm
Tegison (etritinate)	Bone toxicity
Orlaam (levomethadyl)	Serious cardiac adverse events
Vioxx (rofecoxib)	Myocardial infarction, stroke
Bextra (valdecoxib)	Fatal cardiovascular events
Tysabri (natalizumab),	Progressive multifocal leukoencephalopathy (PML)
Trasylol (aprotinin)	Renal toxicity
Permax (pergolide)	Serious damage to patients' heart valves
Zelnorm (tegaserod maleate)	Myocardial infarction, stroke, angina
Meridia (sibutramine)	Increased risk of heart disease
Raptiva (efalizumab)	Progressive PML
Mylotarg (gemtuzumab ozogamicin)	Death
Cylert (pemoline)	Life-threatening hepatic failure
Neutrospec (technitium (99 m tc) fanolesomab)	Serious and life-threatening cardiopulmonary events

Results

Of 15 drugs considered for this analysis, reviews from original NDA approvals were available for only 7 drugs on the FDA websites as described in the Methods section. Those 7 drugs were Vioxx® (rofecoxib), Bextra® (valdecoxib), Meridia® (sibutramine), Zelnorm® (tegaserod maleate), Raplon® (rapicuronium), Mylotarg® (gemtuzumab), and Baycol® (cerivastatin), hereafter referred to only by their brand names.

For 5 drugs, Baycol, Mylotarg, Zelnorm, Bextra, and Vioxx, no evidence was found in the NDA databases that might have foreshadowed the eventual drug withdrawals (Table 2).

The NDA data for Meridia and Raplon, however, contained data that might have predicted the adverse drug reactions (ADRs) seen during marketing of the drug, which caused the eventual market withdrawal.

Meridia (Sibutramine)

Meridia was an oral anorexic agent manufactured by Abbott Laboratories. It was intended for treatment of exogenous obesity (weight loss in certain obese people with heart disease or maintenance of weight loss in obese people). It was approved by the FDA in 1997. Because of several safety issues such as

Table 2. Drugs withdrawn from the market for which no evidence of later problems were discovered in the New Drug Application (NDA) reviews.

Brand Name	Reasons for Market Withdrawal	Retrospective Analysis of Incidence of Adverse Events in NDA Safety Databases
Bextra	Fatal cardiovascular events	No significant difference from placebo for these events
Zelnorm	Myocardial infarction, stroke, angina	No significant difference from placebo for these events
Mylotarg	Lack of efficacy; death	Few deaths occurred in patients but not attributed to the drug
Baycol	Rabdomylosis	No significant difference from placebo for these events
Vioxx	Myocardial infarction, stroke	No significant difference from placebo for these events

Information derived from FDA MedWatch[3] and medical officers' reviews (see Methods).

Table 3. Number of permanent dose reductions by initial dose of sibutramine.

	Placebo (n = 148)	1 mg (n = 149)	5 mg (n = 151)	10 mg (n = 150)	15 mg (n = 152)	20 mg (n = 146)	30 mg (n = 151)
Adverse event	3	7	4	10	6	15	23
Blood pressure	5	1	1	4	6	5	13
Pulse rate	1	1	2	0	4	11	4
Other	0	1	6	3	4	1	4
Unknown	0	0	1	1	0	1	1
Total	9	10	14	18	20	33	44
Percentages	6	7	9	12	13	23	29

US Food and Drug Administration, Center for Drug Evaluation and Research.[7]

Table 4. Comparison of cardiovascular adverse events associated with Meridia and placebo use.

Adverse Event	Meridia (n = 1766)	Placebo (n = 605)
Tachycardia	2.5%	0.5%
Palpitations	3.1%	1.2%
Hypertension	2.1%	0.8%
Vasodilation	2.6%	0.8%

US Food and Drug Administration, Center for Drug Evaluation and Research.[7]

serious cardiovascular events and a16% increase in risk of heart attack and stroke compared to the premarketing clinical trial period,[5] it was removed from the US market (FDA-initiated decision) in 2010.[6]

Placebo-controlled trials with dexfenfluramine as an additional control group were included in the NDA approval package.[7] Issues found in the FDA medical review included premature discontinuations, dose reductions due to adverse events (AEs), cardiovascular AEs, deaths, withdrawal due to AEs, and blood pressure changes. Dose reduction occurred as a result of an intolerable AE, or systolic blood pressure being greater than 160 mm Hg, or diastolic blood pressure being greater than 95 mm Hg.[7] The percentage of patients who underwent dose reductions as a result of the adverse effects is displayed in Table 3.[7]

The percentage reduction in subjects taking 10-, 15-, and 20-mg doses of Meridia were 12%, 13%, and 23% when compared to 6% in the placebo-treated subjects. Overall, the permanent dose reduction numbers found in study BRI 852 was about 7.2% of the study population. The common adverse events responsible for these dose reductions were hypertension, tachycardia, chest pain, anxiety, and anorexia.

Cardiovascular AEs were a concern during drug development. The cardiovascular AEs associated with the Meridia included arrhythmias, ventricular ectopic beats, atrial fibrillation, left bundle branch block, and T-wave changes. Cardiovascular adverse events in Meridia and placebo groups are summarized in Table 4[7]

Patients on Meridia had considerably higher incidences of cardiovascular AEs when compared to patients using the placebo. Cardiovascular AEs were the key factors responsible for the eventual market withdrawal of Meridia.

Of the electrocardiograms (ECGs) measured in 2473 participating subjects, 31 of them were abnormal.[7] Of these, 3 of them were seen in the placebo-treated patients and the remaining 28 were seen in Meridia-treated subjects. Among those 28, 5 of them were considered clinically significant.[7]

Withdrawal of subjects from the study due to AEs was also considered. About 9.9% of the subjects taking Meridia withdrew from the study, while 8.4% of placebo subjects withdrew. All the subjects who withdrew from the Meridia treatment suffered from nervous system or cardiovascular AEs.

Table 5. Comparison of mean changes from baseline in blood pressure in Meridia (different doses) and in placebo-treated subjects.

		Meridia						
BP measurement, mmHg	Placebo	<5 mg	5-9 mg	10-14 mg	15-19 mg	20-29 mg	>30 mg	All Doses
Resting SBP	–0.7	0.1	2	1	2.7	1.7	4	1.7
Standing SBP	0.9	1.2	1.1	3.1	3.3	3.5	1.2	2.3
Resting DBP	–0.6	–0.1	1.5	1.4	1.8	2.2	3.1	1.5
Standing DBP	0.5	–1.3	0.6	1.7	4	2.6	2.3	1.7

US Food and Drug Administration, Center for Drug Evaluation and Research.[7] SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 6. Patient discontinuations due to adverse events.

	Discontinuation by Type of Patient		
	Normal Obese (n = 2319)	Obese Hypertensive (n = 126)	Obese Diabetic (n = 96)
Placebo	8.4%	2.7%	4%
Meridia	10.2%	4.2%	6.8%

Source: US Food and Drug Administration, Center for Drug Evaluation and Research.[7]

Table 7. Comparison of bronchospasm occurrences in different drug-treated subjects.

Drug Name	Bronchospasm Occurrence
Raplon (n = 564)	4%
Succinylcholine (n = 177)	2.1%
Placebo (n = 84)	1.2%

MedWatch: The FDA Safety Information and Adverse Event Reporting Program.[8]

The mean change from baseline in systolic blood pressure and diastolic blood pressure in uncomplicated obese patients in placebo-controlled studies by dose is presented in Table 5 as summarized in the FDA review.[7] Dose-related increases in blood pressure were evident.

Premature discontinuations due to adverse events from a clinical trial are usually a measure of drug safety and drug compliance. The percentage of subjects discontinued without completing the study because of AEs is presented in Table 6. The percentage of discontinuations was higher in subjects receiving Meridia when compared to the placebo.

The approved labeling of Meridia at the time of NDA approval (2001) included the following warning: "Elevations in the blood pressures can be caused by the usage of this drug and monitoring of the vital signs for the treated patients should be done by the physicians. Meridia should not be given to the patients with uncontrollable blood pressures. Patients with concomitant cardiovascular disease should not take Meridia as there is a possibility of elevation of disease status."

Raplon (Rapicuronium)

Raplon was a drug used in anesthesia to enable endotracheal intubation. It was manufactured by Organon Company and approved by FDA in 1999. Raplon was voluntarily withdrawn from the US market in 2010 because of serious side effects such as bronchospasm and unexplained fatalities.

The NDA approval of this drug was mainly based on safety data from study ORG 9487.[8] Issues raised during the review included bronchospasm, histamine levels, adverse events, and the effect of concomitant medications. The major AEs discovered during NDA submission were bronchospasm, hypotension, and tachycardia.

Bronchospasm is a high-risk respiratory disorder in which a sudden constriction of the muscles in the walls of bronchioles occurs; it is mainly caused by the release of histamines. Bronchospasm was one of the major AEs in NDA safety reports of Raplon (Table 7). The incidence of bronchospasm in Raplon-treated subjects was $\sim$4 times that of placebo-treated subjects and twice that of succinylcholine-treated subjects. Abnormal levels of histamine in the body can lead to bronchospasm, hypotension, and errythmetic rash.[8] According to the NDA safety database, a dose-related histamine level elevation is observed in the Raplon treated patients.[8]

According to the FDA safety databases, an additional reason for the withdrawal of Raplon was a number of unexplained interactions with different drugs. In US studies, subjects taking concomitant vasoactive agents had an increased incidence of bronchospasm and hypertension compared to subjects not taking these agents (9.1% vs 4.6% and 11.4% vs 7.2%). In the NDA database, Raplon was linked to a significant elevation of bronchospasm incidents in the case of subjects taking vasoactive agents and anti-asthmatics. Anesthetics like propofol, thiopental, and fentanyl, when interacting with Raplon, have been shown to cause bronchospasm during NDA studies. When comparing patients taking anesthetics and Raplon with patients taking just anesthetics, the ratio of bronchospasm incidents is 5.6%:0%. In the same situation, the ratio of tachycardia incidents is 4.8%:0%.[8]

Table 8. Comparison of incidence of hypotension and bronchospasm in different age group subjects treated with Raplon or succinylcholine.

		Incidence by Age Group, n (%)			
Drug Name	Adverse Event	18-30 Years	31-40 Years	41-50 Years	51-64 Years
Raplon (n = 564)		n = 130	n = 161	n = 129	n = 144
	Hypotension	3 (2.3)	5 (3.1)	7 (5.4)	28 (19.4)
	Bronchospasm	11 (8.5)	9 (5.6)	3 (2.3)	2 (1.4)
Succinylcholine (n = 177)		n = 46	n = 54	n = 45	n = 32
	Hypotension	1 (2.2)	4 (7.4)	5 (11.1)	8 (25)
	Bronchospasm	0.0	0.0	1 (2.2)	1 (3.1)

MedWatch: The FDA Safety Information and Adverse Event Reporting Program.[8]

Table 9. Frequency of various adverse events (AEs) in Raplon-treated subjects.

	Frequency of AE		
System Organ Class AE	In Adults and Geriatrics (n =596)	In Children (n = 17)	In Infants (n = 72)
Gastrointestinal	5.7%	5.9%	2.8%
Heart rate and rhythm	5.7%	11.8%	1.4%
Tachycardia	3.7%	11.8%	
Respiratory	15.8%	17.6%	11.1%
Bronchospasm	10.9%	5.9%	4.2%
General	0.8%	5.9%	5.6%
Application site reaction	0.7%	35.3%	29%

MedWatch: The FDA Safety Information and Adverse Event Reporting Program.[8]

Incidences of common AEs caused by Raplon and by succinylcholine are summarized in Table 8. The frequency of various AEs in Raplon-treated subjects may be found in Table 9.

The approved labeling for Raplon included the following warning: "The usage of Raplon may sometimes result in hypersensitivity reactions and anaphylactic reactions." Clear instructions were provided about the drug interactions in case of concomitant drug usage. Bronchospasm was described as a very low frequency AE. Bronchospasm, however, was the main AE that led to the voluntary withdrawal decision by the manufacturer of Raplon. During the clinical trials the occurrence of bronchospasm was 3.2%; this percentage was exceeded during marketing for the same dose. Other unexplained fatalities were also seen postmarketing.[9]

Discussion

Based on the analysis of the withdrawn drugs during the period 2001-2010, the majority of events that led to market withdrawal were not predictable from the NDA databases. While a small number of withdrawals might have been predicted based on a retrospective analysis of NDA databases, preliminary analyses suggest that the majority of the drug withdrawals could not have been prevented.

The key events that led to Meridia's withdrawal from the market were foreshadowed by the events in the NDA database. After completing the initial NDA review, the Medical Officer recommended against the approval of Meridia due to an unsatisfactory risk-benefit ratio (clinically significant rise of the blood pressure). The sponsor was advised by FDA to provide additional information regarding the issues related to increase in blood pressure and its maintenance, change of initial treatment dosage and development of patient Medication Guide on blood pressure, and other related issues. In response to FDA request, the sponsor provided additional clinical data that showed clinically meaningful weight loss (satisfying FDA weight loss criteria). The sponsor described the risk-versus-benefit ratio of Meridia as:

> Obesity has high excess mortality of 1168 per million per year. Sibutramine treatment, adjusted for the lack of lowering of blood pressure will save 235 lives per million per year. While sibutramine risk related to an increase in mean blood pressure of 2 mm Hg is estimated to be 32 per million treated per year. The net benefit of treatment, 203 lives is a 9% reduction in mortality. Risk may be lowered and benefits enhanced by clinical monitoring and treatment only of responders.[i]

The sponsor lowered the initial treatment dose to 5 mg. (It was 15 mg prior to the initial NDA submission.) The labeling of

Meridia clearly mentioned the risk of increase in blood pressure (associated cardiovascular disease) and a recommendation to avoid use in the patients with concomitant cardiovascular disease and uncontrollable blood pressures. The labeling also advised close monitoring of blood pressure by physicians. Thus, the drug was approved as it was determined that the benefit of its usage outweighed its risks. The sponsor was also required to conduct Phase 4 trials for testing the long-term effects of Meridia's use. The decision to withdraw Meridia was related to the data from these long-term clinical studies. Findings from these studies showed that cardiovascular risks outweighed the minimal benefits.[ii] The data from the original NDA clearly showed potential risk of long-term use; when combined with the minimal reduction in weight, it was determined the risk-benefit ratio was not positive. Given the modest reduction in weight loss seen in the NDA, it is hard to calculate a positive risk-benefit ratio even at product launch.

For Raplon, bronchospasm was a known AE even before the drug's approval. According to the labeling at product launch, there was no mention of any potential occurrences of bronchospasm connected to the use of Raplon, which was a known AE and became the primary reason for its withdrawal. If labeling had contained warnings of bronchospasm, perhaps the number of fatalities might have been reduced. However, given the modest benefit and high risk seen in the NDA database, the benefit-risk ratio at the time of NDA approval was likely not positive.

While this analysis has the advantage of hindsight, a close examination of these two NDA safety databases gave rise to questioning the wisdom of the approval for 2 out of 7 drugs later withdrawn from marketing. Thus, for less than 30% of drugs for which data were available, there was some hint of possible problems. Fifteen drugs were withdrawn in the time period 2001-2010 while the number of drugs approved in the same period was 200. The rate of withdrawal was therefore 7.5%. While a favorable NDA risk-benefit analysis cannot always assure a favorable risk-benefit analysis once the drug reaches the marketplace, drugs with questionable favorable profiles at time of NDA submission require special scrutiny prior to approval. If these estimates can be extrapolated to the universe of drug approvals, of the total percentage of drugs that are withdrawn from the marketplace, perhaps less than 30% could have been prevented with a more conservative review, although the remaining nearly 70% could not have been predicted from the NDA databases.

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Note

i. From the concluding slide of a July 25, 1996 meeting between Knoll and the FDA. Contained in FDA Approval Documents (see Methods), "Administrative Documents."

ii. Data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) led FDA to make the withdrawal decision on Meridia. The main objective of the study was a postmarketing review of the cardiovascular safety of sibutramine. This duration of the study was approximately 7 years and had an enrollment of ~10,000 overweight or obese patients with diabetes or a history of coronary or peripheral vascular disease or stroke, along with other cardiovascular risk factors. The results of this study showed an increase of the risk of cardiac fatalities by 16% when compared to placebo.[10]

References

1. US Food and Drug Administration, Center for Drug Evaluation and Research. Report to the nation. Improving public health through human drugs. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM079006.pdf. Published 2000. Accessed August 28, 2011.
2. US Food and Drug Administration, Federal Register. List of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness. https://docs.google.com/document/d/1ELc_v5v0FqjLH-G7JbaHC2utrbwDcsDK70F8dfDuVSw/edit?hl=en_US&pli=1. Published October 8, 1998. Accessed August 21, 2011.
3. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm. Published 2011. Accessed August 19, 2011.
4. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. 2010 Safety alerts for human medical products. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196258.htm. Published 2010. Accessed August 2011.
5. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Voluntary market withdrawal Re: RAPLON® (rapacuronium bromide) for injection. http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173891.pdf. Published March 20, 2001. Accessed June 9, 2012.
6. US Food and Drug Administration. Drug approval package: Meridia (sibutramine hydrochloride monohyrdate) capsules. http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20632_meridia.cfm. Published May 22, 2003. Accessed August 18, 2011.
7. US Food and Drug Administration, Center for Drug Evaluation and Research. CDER drug approval package for Meridia. http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf. Published May 22, 2003. Accessed August 18, 2011.

8. US Food and Drug Administration, Center for Drug Evaluation and Research. CDER drug approval package for Raplon. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20984_RAPLON_me dr_P3.pdf. Published July 2, 2001. Accessed August 22, 2011.
9. US Food and Drug Administration. Postmarket drug safety for patients and providers. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm191650.htm. Published February 22, 2010. Accessed June 9, 2012.
10. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Meridia (sibutramine): market withdrawal due to risk of serious cardiovascular events. http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm228830.htm. Published January 21, 2010. Accessed June 9, 2012.