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THE COMPETITIVE EFFECTS OF DRUG WITHDRAWALS: THE CASE OF FEN-PHEN

John Cawley
John A. Rizzo

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ABSTRACT

In September 1997, the anti-obesity drugs Pondimin and Redux, ingredients in the popular drug combination fen-phen, were withdrawn from the market for causing potentially fatal side effects. That event provides an opportunity for studying how consumers respond to drug withdrawals. In theory, remaining drugs in the therapeutic class could enjoy competitive benefits, or suffer negative spillovers, from the withdrawal of a competing drug. Our findings suggest that, while the withdrawal of a rival drug may impose negative spillovers in the form of higher patient quit rates, on the whole non-withdrawn drugs in the same therapeutic class enjoy competitive benefits in the form of higher utilization.

John Cawley
134 MVR Hall
Department of Policy Analysis and Management
Cornell University
Ithaca, NY 14853
and NBER
jhc38@cornell.edu

John A Rizzo
Department of Economics and
Department of Preventative Medicine
N-637 Social and Behavioral Sciences Building
Stony Brook University
Stony Brook, NY 11794
john.rizzo@stonybrook.edu

Introduction

The withdrawal of prescription drugs from the U.S. market is a relatively frequent phenomenon; more than 75 drugs have been withdrawn since 1969 (Wysowski and Swartz, 2005).[2] Some of the more recent withdrawals have been of prominent drugs that represented a large share of the market in their respective therapeutic classes. For example, in 1997 the Food and Drug Administration requested that Wyeth remove from the market its anti-obesity drugs Pondimin and Redux that had been used by six million Americans because the drugs caused potentially fatal valvular heart disease (Connolly et al., 1997; Agovino, 2004).[3] In 2004, Merck withdrew the pain medication Vioxx, used by an estimated 20 million Americans, for increasing the risk of heart attack and stroke (Agovino, 2004).

This paper studies the withdrawals of seven drugs from six therapeutic classes between 1997 and 2001 and answers the following questions: Do remaining drugs in the same therapeutic class enjoy competitive benefits or suffer negative spillovers? Do those taking drugs in the class that were not withdrawn reduce compliance or quit? Do people who previously took the withdrawn drugs quit taking that class of drugs altogether? Are people less likely to initiate use of non-withdrawn drugs following the withdrawal of a therapeutically equivalent drug? On net, how does utilization of the non-withdrawn drugs change? The answers to these questions have important implications for understanding

[2] The roughly 75 drugs withdrawn between 1969 and 2002 represent about 1 percent of all marketed drugs (Wysowski and Swartz, 2005).

[3] Although the Food and Drug Administration *requests* that a manufacturer withdraw a drug from a market, the FDA can mandate the withdrawal if necessary. When asked by the FDA to withdraw a drug because of safety concerns, manufacturers have agreed in all cases except one: Ceiba-Geigy refused to voluntarily withdraw the antidiabetic drug phenformin in 1976. If a company refuses the FDA's request, the FDA can begin procedures to compel withdrawal, and it was through this process that phenformin was taken off the market (Meadows, 2002). All of the drug withdrawals that we study were removed from the market voluntarily by the manufacturer.

the nature of competition in the pharmaceutical industry and for assessing the economic effects of drug withdrawals. Moreover, the existence of spillover effects can provide important insight into how drugs compete and how product markets should be defined.

The present study is timely, given recent withdrawals of "blockbuster" drugs such as Vioxx in 2004 and Bextra in 2005, and the potential for additional withdrawals in the near future. In November 2004, the U.S. Food & Drug Administration's David Graham questioned whether additional drugs (Meridia, Crestor, Accutane, and Serevent) should be withdrawn from the market (Harris, 2004). These developments highlight a pressing need to understand how consumers respond, and the use of remaining drugs changes, in the wake of drug withdrawals.

To our knowledge, this is the first direct study of consumer response to drug withdrawals. Moreover, the related literature implies divergent predictions. Studies of short-run changes in the stock prices of rival firms following drug withdrawals have found evidence of both positive and negative effects (Jarrell and Peltzman 1985; Dowdell et al. 1992; Ahmed et al. 2002).

This paper extends the literature by offering a direct, longer-term test of the impacts of drug withdrawals on spillovers. In addition, the study documents *how* consumers respond to the withdrawal of a prescription drug by measuring spillover effects on new initiations of drug therapy, quit rates, and the utilization of non-withdrawn drugs.

We study a nationally representative patient-level database from the Medical Expenditure Panel Study for 1996 through 2002. We find that results vary across drug class, with the largest number of classes exhibiting some evidence of negative spillovers.

We then discuss which factors may affect whether remaining drugs enjoy competitive benefits or suffer negative spillovers.

Conceptual Framework

Our conceptual framework is straightforward. The withdrawal of a drug from the market could result in either competitive benefits or negative spillovers to the remaining drugs in the same therapeutic class. One might expect competitive benefits to the extent that the drugs in a given therapeutic class represent an oligopoly. Entry is regulated by the FDA and is very costly in time and money. The withdrawal of one competitor increases the residual demand, and therefore equilibrium quantity supplied, by remaining producers.[4] If this increase in sales offsets the loss of previous customers who quit because of the withdrawal of the related drug, the remaining drugs enjoy competitive benefits.

Several studies in finance have tested whether competitive benefits dominate negative spillovers by examining how pharmaceutical firms' share prices change in the wake of bad news about a competitor's product. Ahmed, Gardella and Nanda (2002) find that competitors' share prices rose significantly five days after the announcements of drug withdrawals that occurred between 1966 and 1998. Dowdell, Govindaraj, and Jain (1992) find that in the wake of the Tylenol poisonings, the share prices of rival pharmaceutical manufacturers rose relative to the share price of the manufacturer of Tylenol (Johnson & Johnson).

On the other hand, one might expect negative spillovers to dominate any competitive benefits. Negative spillovers arise if, for example, consumers become

[4] Overall sales of the class could fall even if sales of the remaining drugs are higher after the withdrawal.

concerned about the safety of the entire class of drugs and decrease their utilization of the non-withdrawn drugs to such an extent that those quits exceed the number of patients switching from the withdrawn to the non-withdrawn drugs. Jarrell and Peltzman (1985) study drug withdrawals during 1974-1982 and find evidence of net negative spillovers; specifically, the share prices of pharmaceutical companies fall an average of 1 percent in the two weeks surrounding the announcement of bad news that led to the withdrawal of a rival drug.[5]

Interestingly, some stock price studies of drug withdrawals find competitive benefits (Ahmed et al., 2002; Dowdell et al. 1992) while another finds negative spillovers (Jarrell and Peltzman, 1985). A further study finds no net effect of drug withdrawals on the share prices of rival pharmaceutical firms (Dranove and Olsen, 1994).

These studies of stock price changes following drug withdrawals are informative about investor beliefs (e.g. about changes in the likelihood of regulation or FDA scrutiny of future drugs) but may not reflect changes in actual drug utilization patterns. Moreover, the follow-up period of these studies (ranging from days to weeks) is too brief to assess long term trends following withdrawals. The fact that the studies come to divergent conclusions about spillovers underscores the need for a direct study of consumer behavior following drug withdrawals.

This paper makes a number of contributions to the literature on the competitive effects of prescription drug withdrawals. First, it is the only direct study of how consumers respond to drug withdrawals. Earlier research has focused on investor beliefs,

[5] Examples from outside the pharmaceutical industry in which the negative spillovers of information dominated competitive benefits include: decreases in the prices of shares for airlines after a crash by a competing airline (Bosch, Eckard, and Singal, 1998) and decreases in the price of shares for nuclear energy firms after the 1979 core meltdown at the Three Mile Island nuclear power plant (Hill and Schneeweis, 1983).

not consumer behavior. Second, this paper uses multiple measures to study competitive effects, including drug utilization, initiations, and quits of non-withdrawn drugs in response to withdrawals in the same class. This approach recognizes the multidimensional nature of competitive responses and provides a sense of the robustness of the results to alternative competitive outcome measures. Third, this paper uses a longer follow-up than previous studies of stock prices; we track consumers from up to three years before to three years after a drug withdrawal. Fourth, it provides a test of whether drugs within the same therapeutic class constitute a product market. While drug product markets are conventionally defined in terms of whether drug utilization patterns respond to significant changes in competitors' prices or other competitive variables,[6] in practice such changes are often difficult to observe. Studies have found evidence that brand name drugs within the same therapeutic class compete, however. Thus, Lichtenberg and Philipson (2002) find that changes in the number of drugs in a therapeutic class affect utilization of drugs within that class. Lu and Comanor (1998) report that a brand's intertemporal rate of price increase was lower when there were more branded competitors in the market.[7] Our study contributes to this literature by providing six natural experiments to investigate whether utilization patterns of drugs within a therapeutic class are linked to the withdrawal of another drug within that class.

This paper also relates to a literature in pharmaceutical economics on how consumers respond to information. Studies of the pharmaceutical industry most

[6] More specifically, in defining product markets, the Department of Justice guidelines recommend that all relevant information be considered, including "evidence that sellers base business decisions on the prospect of buyer substitution between products in response to relative changes in price or other competitive variables…" See: www.usdoj.gov/atr/public/guidelines/horiz_book/01.html at section 1.11.

[7] For a review of the evidence on competition between brand-name drugs see: Congressional Budget Office (1998): *How Increased Competition from Generic Drugs has Affected Prices and Returns in the Pharmaceutical Industry, ch. 3* (available at www.cbo.gov/showdoc.cfm?index=655&sequence=0).

commonly focus on the impact of advertising on the sales of the drug that was advertised (Azoulay, 2002; Calfee, et al., 2002; Rizzo, 1999; Berndt et al., 2002, 1995; Hurwitz and Caves, 1988; Leffler, 1981). However, recent research documents how the benefits of advertising may spill over to other drugs in the same therapeutic class. For example, direct-to-consumer advertising (DTCA) for one drug increases the sales of the entire class of drugs (Rosenthal et al., 2003; Iizuka and Jin, 2003).[8] DTCA also appears to have spillover benefits at the intensive margin: DTCA of one drug increases compliance among users of other drugs within the same therapeutic class (Wosinska, 2003, 2004). In addition, marketing for prescription drugs has positive spillover effects for same-brand over-the-counter (OTC) versions of the drugs, although DTCA for OTC products do not appear to spill over to same brand in the prescription drug market (Ling, Berndt, and Kyle, 2002). Other research has focused on how physician prescribing behavior responds to various types of information, such as detailing and the results of clinical trials published in professional journals (Azoulay, 2002; Stern and Trajtenberg, 1998). We contribute to this literature by studying how pharmaceutical consumers respond to bad news in general and a drug withdrawal in particular.

Methods

Ideally, we would like to compare the market for a particular therapeutic class of drugs after a withdrawal in the class to its counterfactual: how that same market would look in the same years if the drug had not been withdrawn. Obviously, such information is unavailable. Nor is there any satisfactory "control" group in the form of a therapeutic

[8] DTCA appears to increase the advertised drug's market share within the class only if that brand has preferred status on the third-party payer's formulary (Wosinska, 2001).

class with identical trends in unobserved variables but no drug withdrawals (which would permit estimation of a differences-in-differences model).

Therefore, we study the impact of prescription drug withdrawal by comparing the consumer use of competing drugs before withdrawal to consumer use of them after withdrawal, controlling for salient observables. One key observable is the number of scrips for all prescription drugs filled, per capita, by year in the respondent's geographic region; this regressor is particularly important because during the period we study (1996-2002) there was a general upward trend in the use of pharmaceuticals in the U.S. (Banthin and Miller, 2005; Berndt, 2002). Failure to control for this trend would bias our results in favor of finding competitive benefits.[9]

A limitation of our empirical strategy is that there may be trends in unobserved variables that changed specific drug markets around the time of the drug withdrawal; in other words, there may be omitted variable bias. We believe that such bias is likely to be relatively modest. Drug withdrawals are generally extremely well-publicized and are likely the dominant event in their therapeutic classes. For example, the withdrawal of fen-phen was accompanied by editorials in the *New England Journal of Medicine* and *JAMA* and prominent coverage in virtually all major U.S. newspapers (the *Los Angeles Times* won a Pulitzer Prize for its coverage of the withdrawal of Redux).

In addition, we look for common patterns across six drug classes in which a withdrawal occurred between 1997 and 2001. If we see the same pattern across all six drug classes, we can be more confident that it is due to the withdrawals than due to

[9] Another potentially important unobservable is the change in the FDA's policy allowing direct-to-consumer advertising, which occurred during the period of our study. This provides a further motivation for controlling for scrip use over time to the extent that this policy change affected drug use. We thank an anonymous referee for calling this point to our attention.

random chance that unobserved changes happened to occur in each class around the time of withdrawal (which ranges across markets from 1997 to 2001).

While our model does not control for the prices of anti-obesity drugs or advertising expenditures on such drugs, for our purposes these variables do not cause omitted variable bias. The reason is that we consider how the manufacturers of remaining drugs changed their price and advertising strategies in the wake of drug withdrawal to be part of the overall impact of drug withdrawal and thus these influences do not represent bias but part of what we wish to measure.

We estimate three types of models: 1) *utilization*, in which the binary dependent variable equals one if the respondent is using a non-withdrawn drug in that class in that year[10]; 2) *initiation*, in which the binary dependent variable equals one if the respondent reports using a non-withdrawn drug in the current interview but did not report using one in the previous interview[11]; and 3) *quit*, in which the binary dependent variable equals one if the respondent reported using a non-withdrawn drug in the previous, but not the current interview. The utilization, initiation, and quit equations are estimated as logit models.

The coefficients on year indicator variables provide information about the net effect of the drug withdrawals on remaining drugs. Specifically, we compare the year

[10] If utilization were the only outcome in which we were interested this could be measured roughly by using aggregate sales data. However, we also wish to test how drug withdrawals affect initiations and quits, and this requires longitudinal micro data. Even with respect to utilization, we wish to control for correlates of demand such as income and insurance status, which also requires micro data.

[11] There are several steps involved for a patient to receive a prescription drug. First, the patient must decide to visit a physician. Second, the physician must determine whether to prescribe any drug, and then which drug to prescribe. Third, the patient must decide whether to fill the prescription. We set aside explicit consideration of the agency relationship between consumer and physician and study consumer use of drugs as an outcome; thus our results reflect consumer behavior under the average agency relationship.

prior to drug withdrawal to years after drug withdrawal (the year of withdrawal is a mixture of pre-treatment and post-treatment and so is not the primary focus).

In the MEPS data, the number of people with a given condition may fluctuate by chance with the selection of new MEPS sample members. Moreover, there have been trends over time in some conditions; for example, obesity has doubled in the past twenty-five years in the U.S. (Hedley et al., 2004). To control for changes in the conditions of sample respondents over time, we control in our models for an indicator variable that equals one if the respondent has the condition treated by the class of drugs under consideration.

We control for the following variables in our regressions: the trend in per capita number of scrips in respondent's geographic area, indicator variables for year, whether the respondent has the condition treated by that class of drugs, gender, African-American, Hispanic, other race/ethnicity, married, whether the respondent has health insurance, whether the respondent's health insurance includes prescription drug coverage, age categories, urban residence, Census Region categories, income categories, and education categories.

Data and Empirical Specification

This paper uses 1996-2002 data from the Medical Expenditure Panel Survey (MEPS), which is collected by the Agency for Healthcare Research and Quality (AHRQ). The MEPS database is drawn from the National Health Interview Survey (NHIS) sample, so it is designed to be nationally representative and each year of the MEPS data may be linked to information from the previous year's NHIS survey. The MEPS database has a complex

survey design which, beyond stratifying by sampling units, includes clustering, and oversampling of certain subgroups such as minorities. Therefore, our statistical analyses use weights provided in MEPS to correct mean values, and appropriate statistical methods in Stata to obtain correct standard errors.

The MEPS has an overlapping panel design in which two calendar years of information are collected from each household through six interviews. We pool both calendar-year observations on each adult (age 18 and older) and pool years 1996 to 2002. Our final sample is 124,314. We use the first of two calendar years of MEPS data on each person in order to determine whether in the second period the person has initiated or quit using a relevant drug. As a result, we lose half of our data when we estimate models of initiation.

The MEPS database consists of a number of files. We linked the Full Year Consolidated File to the Prescribed Medicines File for each year. The Full-Year Consolidated File is at the person-year level and includes information on health care utilization and expenditures, sociodemographic and socioeconomic characteristics, and health insurance status. The Prescribed Medicines File is an event-level file that includes information on specific drug use, the amounts paid for those drugs by patient and insurers, and the length of time that the drug was taken. We convert this event-level data into person-year data and link it to the consolidated MEPS files, which include patient-year level information on the other variables included in this analysis.

Given the way the MEPS data are collected, we must study consumer utilization of drugs by calendar year; for example, we are not able to study quits in the same year that the withdrawals occurred. The reason is that the MEPS asked respondents to list all

drugs taken since the last interview up to the end of the year. So even though Redux and Pondimin were withdrawn in September of 1997, any MEPS respondents who had used anti-obesity drugs prior to the withdrawal were still listing them even if they were interviewed in October through December of 1997. Quits can only be ascertained in the next calendar year.

We study the seven drugs from six therapeutic classes that were withdrawn between 1997 and 2001 that are listed in Table 1. Pondimin and Redux, both anti-obesity drugs, were withdrawn in 1997 for causing valvular heart disease. Duract was a pain medication withdrawn in 1998 for causing liver failure. Posicor was an anti-hypertensive drug also withdrawn in 1998 for lowering heart rates and causing adverse drug interactions. Propulsid was a heartburn medication withdrawn in 2000 for causing potentially fatal irregular heartbeat. Lotronex treated Irritable Bowel Syndrome (IBS) and was withdrawn in 2000 for causing ischemic colitis (intestinal inflammation due to lack of blood flow). Baycol was a cholesterol-busting drug withdrawn in 2001 for causing fatal rhabdomyolysis (severe adverse muscle reaction that can damage the kidney and other organs).

We use the Multum Lexicon File, released in Fall 2004, to identify drugs that remain available in the therapeutic class of each withdrawn drug. These drugs that remained on the market, and the name of their therapeutic class, are also listed in Table 1. For the sake of clarity, we will refer to these remaining drugs by the indication that the drugs treat.

We are forced to exclude from our analysis a few other drugs that were withdrawn between 1997 and 2001. We exclude Seldane and Hismanal, both of which treated

seasonal allergies and caused potentially fatal irregular heartbeats, because their withdrawals occurred in consecutive years (1998 and 1999), making it impossible to disentangle the change in utilization due to each withdrawal. Rezulin, a diabetes drug, was withdrawn in 2000 for causing liver failure, but we exclude it from our analysis because it was the only drugs in its class – there were no competitors to suffer spillovers or reap competitive benefits.

We study the following three outcomes: 1) an indicator that equals one if the respondent in that year had a scrip for an anti-obesity drug; 2) an indicator that equals one if the respondent began taking an anti-obesity drug; and 3) an indicator that equals one if the respondent quit taking an anti-obesity drug.

The means of the dependent variables by class are listed in Table 2. Drugs that treat pain are the ones most often used by MEPS respondents; use at some point in a calendar year is reported by 10.8 percent of observations. Hypertension and cholesterol drugs are next most common, used by 6.8 and 6.5 percent of the sample. Drugs that treat obesity, heartburn, and IBS are much less frequently used; only one half of a percent or less of the sample reports their use in a year. (Note that these do not include use of the withdrawn drug in the years prior to withdrawal.)

There exist several measures of, or proxies for, the out-of-pocket price of drugs, each with its advantages and drawbacks. MEPS respondents list the amount they paid out of pocket for each drug, but the prices faced by those who did not buy drugs are not observed. National average wholesale prices are available from Medi-Span, but these are collinear with the year fixed effects. To address patient costs while avoiding problems of multicollinearity, we use two proxies for the out-of-pocket cost of prescription drugs.

The first is an indicator variable for whether the respondent lacked health insurance; uninsurance would raise the cost of a physician visit to receive a prescription. The second price proxy is an indicator for whether the respondent's health insurance includes prescription drug coverage, which would lower the cost of filling a prescription. We acknowledge that these indicators for health insurance coverage are endogenous; those who sought to consume large quantities of prescription drugs might be more likely to acquire health insurance and prescription drug coverage.

We calculate the number of scrips for all prescription drugs filled, per capita, by year in the respondent's geographic area, where the area is defined by MEPS sampling areas. There are 258 such areas, and we calculate the per capita scrips per year for each.

We determine whether the respondent has the condition treated by a given class of drugs using the ICD9 condition codes provided in the MEPS.[12] For obesity, we use the FDA and NIH medical criteria for the use of anti-obesity drugs: a body mass index (BMI) of 30 or greater, or BMI of 27 or higher with at least one obesity-related comorbidity (such as hypertension, hyperlipidemia, type II diabetes, coronary heart disease, or sleep apnea). Body mass index is constructed using self-reported weight and height from the

[12] Specifically, respondents are considered to have pain if they have ICD9 code 204 (joint pain), 205 (back problems), or 84 (headache); hypertension if they have code 98 (hypertension); heartburn if they have code 787 (heartburn and others); IBS if they have code 565 (IBS and others); and to have high cholesterol if they have code 53 (lipid disorders including high cholesterol). There are limitations to the use of ICD9 codes to classify respondents as having the condition treated by a particular drug class. For some ICD9 codes, false positives are a concern: ICD9 53 includes other lipid disorders than high cholesterol. Likewise, the ICD9 codes for heartburn and IBS are broader than we would like. On the other hand, there are likely false negatives for pain; the ICD9 codes permit us only to control for particular sources of pain (back, joint, head). While there are limitations to the use of ICD9 codes to identify respondents with a given condition, they remain the best data for that purpose available in the MEPS.

NHIS corrected for reporting error (Cawley, 2004). For those with a BMI of less than 30, we re-classify them as obese if they have ICD9 code 278 (obesity).[13]

Empirical Results

Tables 3-5 present the results of our regressions for utilization, initiation, and quitting. In the interest of brevity, the tables present only the parameters of interest: the coefficients on the year indicator variables.[14]

Table 3 includes results from logit regressions of utilization. Each cell of the table includes the odds ratio and, below that, the t-statistic in parentheses. The odds ratio indicates the odds of utilizing non-withdrawn drugs in a given class in a given year relative to the year prior to the drug withdrawal. Note that the year prior to drug withdrawal differs by class. For obesity drugs it is 1996, for pain and hypertension drugs it is 1997, for heartburn and IBS it is 1999, and for cholesterol it is 2000. Also note that there are empty cells in the table. Because the MEPS began in 1996, there are data for only one year prior to the withdrawal of Pondimin and Redux in 1997. In contrast, for cholesterol drugs, we have many years prior to the withdrawal of Baycol in 2001, but only one year after withdrawal.

The first row of Table 3, which corresponds to the anti-obesity drugs, provides evidence of negative spillovers. One year after the withdrawal of Pondimin and Redux, MEPS respondents were only 67.3 percent as likely to be taking an anti-obesity drug as they were the year before the withdrawals. These negative spillovers are long-lived; the

[13] We determine obesity-related comorbidities using ICD9 codes, but sleep apnea is not one recorded by MEPS.

[14] The full set of regression results is available from the authors on request.

probability of use is only 66.4 percent as likely two years after withdrawal, and only 43.6 percent as likely three years later. Each of these is statistically significant, and the fact that the odds ratios continue to fall suggests that the negative spillovers may not have run their course even after three years.

There is a similar pattern of negative spillovers for pain medications. One year after the withdrawal of Duract, utilization is only 88.6 percent as likely as it had been the year before withdrawal. Two years later it is only 73.4 percent as likely, and three years it is 68.4 percent as likely.

The utilization of hypertension drugs does not immediately experience a statistically significant change; one year after withdrawal, utilization is 96.1 percent as likely as it was the year prior to withdrawal (which is not statistically significant). However, the decrease in utilization is statistically significant two years after withdrawal (when it falls to 89.3 percent as likely) and three years after withdrawal (89.2 percent as likely).

The pattern of use of IBS drugs is also consistent with negative spillovers, but they quickly dissipate. One year after the withdrawal of Lotronex, use of IBS drugs was only 68.2 percent as likely as it had been the year before withdrawal. The decrease in utilization two years after withdrawal is not statistically significant.

The drop in utilization of non-withdrawn obesity, pain, hypertension, and IBS drugs is consistent with the findings in Jarrell and Peltzman (1985) that the stock price of pharmaceutical firms falls after a drug withdrawal by a rival; presumably the lower stock price reflects decreased anticipated market share due to negative spillovers.

For two other drug classes there appears to be evidence of competitive benefits, which is consistent with the stock price studies of Ahmed et al. (2002) and Dowdell et al. (1992). The use of non-withdrawn heartburn medications is 53.7 percent more likely one year after the withdrawal of Propulsid than the year before withdrawal. The use of cholesterol drugs is 52.3 percent more likely one year after the withdrawal of Baycol than it was the year before withdrawal. However, the pattern of odds ratios across years for these drugs suggests that these results may reflect long-term trends in unobservables rather than the withdrawals. For example, the point estimates of odds ratios for heartburn medications are rising throughout the period observed: from .598 three years before withdrawal to 1 the year before withdrawal (by construction) to 1.408 two years after withdrawal. This pattern suggests that utilization of heartburn medications was rising throughout this period, and therefore the changes observed after withdrawal should not be attributed solely to the withdrawal.

A similar pattern is evident for cholesterol medications. The point estimates of odds ratios rise from .781 three years prior to withdrawal to 1 the year before withdrawal (by construction) to 1.523 the year after withdrawal. For both heartburn and cholesterol drugs, there seems to be a trend towards increasing use over this period; while we control for the trend in scrips per capita by geographic area, the use of cholesterol and heartburn medications may have exceeded that of all drug classes as a whole. As a result of this trend, increases in utilization after withdrawal should not necessarily be interpreted as evidence of competitive benefits.

We next study changes in utilization: initiations and quits. A limitation of these regressions is that we are forced to exclude about half of our data; the MEPS includes

two observations for each person (each corresponding to a calendar year) and the first of those must be used to determine whether the second period represents an initiation or quit. All observations from 1996 must be dropped for this reason. This is a particular problem for studying the obesity drugs, because 1996 is the only year in the MEPS that is prior to the withdrawal of Pondimin and Redux in 1997. As a result, the best we can do for obesity drugs is compare changes in utilization after withdrawal to those the year of withdrawal. This is a limitation. For example, there may have been withdrawal-based initiations of non-withdrawn obesity drugs in 1997 because Pondimin and Redux were withdrawn on September 15, 1997. Thus the treatment effect may already be apparent in our omitted year for obesity drugs. For all other drug classes, dropping 1996 is not a problem because the drug withdrawals in those classes took place in 1998 or later so there remains at least one pre-withdrawal year of data in the MEPS.

Results for initiations of non-withdrawn drugs are provided in Table 4, which reports odds ratios relative to the year prior to withdrawal. There is evidence of negative spillovers in the form of significantly lower initiations post-withdrawal for obesity, pain, and IBS medications. For obesity drugs, initiation of non-withdrawn drugs was only 44.4 percent as likely one year after withdrawal as the year of withdrawal. Initiations remained significantly lower two and three years after withdrawal, with initiation only 33.2 percent as likely three years after withdrawal. These results may overstate the negative spillovers, however. Because many former users of Pondimin and Redux could have switched to non-withdrawn drugs in the year of the withdrawal (the omitted comparison year in this case), initiations in subsequent years may seem small by comparison. However, it is unknown the degree to which the negative spillovers are

overstated. The results for utilization (for which the omitted year was that prior to withdrawal since it did not need to be used to assess the change in utilization) also indicated substantial negative spillovers lasting at least three years, however.

Initiations of pain medications also reflect negative spillovers. Relative to the year before withdrawal, initiations were only 87.7 percent as likely one year after withdrawal, 70.3 percent as likely two years after, and 68 percent as likely three years after. The negative spillovers for IBS drugs are shorter-lived. Only one year after withdrawal is initiation significantly lower (45.8 percent as likely as the year before withdrawal).

Initiations of non-withdrawn hypertension drugs fell to only 69.1 percent of their previous level the year of withdrawal. In subsequent years the odds ratios remain below 1 but the change relative to the year before withdrawal is not statistically significant.

Only one drug class, for heartburn, has results consistent with competitive benefits. One year after withdrawal, the initiation of non-withdrawn heartburn drugs was 160.8 percent more likely than it was the year before withdrawal. There are no statistically significant benefits in the following year (two years after withdrawal), however.

Quits of non-withdrawn drugs are detailed in Table 5. Quits of non-withdrawn obesity drugs rise 113.3 percent the year after withdrawal. One year after that, the change in quits is not statistically significant. No other drug class exhibits negative spillovers in quitting behavior.

In contrast, hypertension and cholesterol drugs appear to enjoy competitive benefits as a result of the withdrawal of a rival drug. Quitting of non-withdrawn

hypertension drugs is only 53.8 to 61.3 percent as likely in any of the three years following withdrawal as it was the year before withdrawal. Quits of non-withdrawn cholesterol drugs are only 70.2 percent as likely one year after as one year before withdrawal. However, the cholesterol results are curious because quitting was also significantly less likely three years before and two years before withdrawal; it may be that by chance (or because news of Baycol's adverse effects was disseminating) the year before withdrawal had an unusually high quit rate and as a result in every other year quits were significantly less likely.

We also examined a special kind of quitting: quitting of the entire class of drugs by those who were taking the withdrawn drugs in the year they were withdrawn. This is a very small subsample of our overall sample, because we can only study those who in their first MEPS observation are taking the withdrawn drug in the year it was withdrawn (and therefore at risk of quitting). Across all drug classes, 70.8 percent of those taking the withdrawn drug in the year it was withdrawn (N=79) did not switch to a drug that remained available in the same class; that is, they quit the entire class. For the two classes with the largest number of observations in this analysis, 48.7 percent of the 37 MEPS respondents who took Baycol in 2001 quit taking any cholesterol drug, and 94.7 of the 19 MEPS respondents who took Pondimin or Redux in 1997 quit taking any anti-obesity drug.

Predicting Negative Spillovers or Competitive Benefits

Our results indicate that there is no definitive pattern following drug withdrawal, though most results point to negative spillovers. In this section we briefly explore what

factors might determine whether a drug class enjoys competitive benefits or suffers negative spillovers. Because the MEPS data cover only seven withdrawals in six classes, we are unable to test our class-level hypotheses, but we can check to see if the results in this paper are consistent with our predictions.

The withdrawal of a drug is expected to impose both gross negative spillovers and gross competitive benefits. The gross negative spillover is that non-withdrawn drugs will lose customers they would have otherwise had as a result of the withdrawal, both in the form of increased quits and decreased initiation; perhaps because the patients fear that the adverse effects of the withdrawn drug are shared by the remaining drugs in the class. The gross competitive benefit is that the non-withdrawn drugs gain some business as a result of the withdrawal; some of those who were previously taking the withdrawn drug will switch to other drugs that remain available in the same therapeutic class after their drug is withdrawn from the market.

In order for there to be competitive benefits on net, the number of former users of the withdrawn drugs who switch to remaining drugs must exceed the number of previous users of non-withdrawn drugs who quit the class plus the number of people who would have initiated use in the absence of the withdrawal but will not initiate because of the withdrawal, or:

$$\text{gross increase} > \text{gross decreases}$$

$$\text{switchers} > \text{additional quits} + \text{lost initiators}$$

$$N_W * (1 - x) > N_{NW} * y + N_{NONE} * z$$

Where N_W is the number of people who were taking the withdrawn drug, N_{NW} is the number of people who were taking the non-withdrawn drugs, and N_{NONE} is the number of people not using any drug in the class (i.e. the number at risk of initiating use). Letting

x denote the percentage of people previously taking the withdrawn drug who quit the class entirely after the drug withdrawal, $(1-x)$ is the percentage of those who previously used the withdrawn drug who switch to a drug that remains on the market in the therapeutic class. The increase in rate of quits of non-withdrawn drugs as a result of the withdrawal is denoted as y, and z is the decrease in the initiation rate of non-withdrawn drugs due to the withdrawal.

According to these equations, competitive benefits are more likely if, *ceteris paribus*, the following conditions hold. First, the number of people taking the withdrawn drug is large relative to the number of people already taking the non-withdrawn drugs in the same class and the number of lost initiators. Competitive benefits are more likely when the withdrawn drug had a high market share because it ensures that a large number of people are at risk of switching to non-withdrawn drugs in the same class. The market share of the withdrawn drugs we study varies dramatically. In the MEPS Prescribed Medicines File, Propulsid represented 57.7 percent of the heartburn medication market at the time it was withdrawn, and Pondimin and Redux jointly represented 46.9 percent of the anti-obesity drug market. In contrast, Lotronex accounted for 8.1 percent of the IBS market, and Baycol for 4.7 percent of the cholesterol drug market. The other two withdrawn drugs had trivial shares of the market: Duract was 1.2 percent of the pain medication market when it was withdrawn, and Posicor was only 0.3 percent of the hypertensive market. The large market shares of withdrawn drugs in the obesity and heartburn markets suggests that we should be more likely to find net competitive benefits of the withdrawals in the obesity and heartburn classes, *ceteris paribus*. In the heartburn class, we do in fact find evidence of net competitive benefits in the overall utilization

(Table 3) and initiation (Table 4). However, for obesity drugs we find strong evidence of net negative spillovers in those same two outcomes.

We also find evidence of negative spillovers in overall utilization and initiation for two classes in which the withdrawn drug had small market share: pain and hypertension medications. Duract and Posicor were used by so few that the number switching from them to non-withdrawn drugs in the same class was insufficient to offset the quits of non-withdrawn drugs. In both cases, overall utilization of non-withdrawn drugs fell after withdrawal.

However, market share of the withdrawn drug is not the only variable that matters. Competitive benefits are more likely the smaller are x (the percentage of previous users of the withdrawn drug that quit the entire class after withdrawal), y (the increase in rate of quits by users of non-withdrawn drugs after withdrawal), and z (the decrease in initiations of non-withdrawn drugs after withdrawal). Each of these may be more likely when the remaining drugs are perceived by consumers and physicians to be unlikely to share the adverse health events that led to the withdrawal of the other drug in the class, when the remaining drugs are especially efficacious, or when there exist few over-the-counter or non-pharmacologic treatments for the condition. While we do not have quantitative measures of these factors, we consider this to be an important direction for future work, so the FDA can better predict how consumers will respond if they withdraw a given drug from the market.

Generalizability

Several factors should be considered when generalizing the results associated with these drug withdrawals to other classes. First, the withdrawal of Redux and Pondimin was extremely well-publicized and this may have led to greater response by consumers than is typical.

Second, one non-withdrawn obesity drug, phentermine, was both a substitute to and a complement for the withdrawn drugs. It was a substitute because it could be prescribed in the place of Redux or Pondimin, but was also a complement in that it was the other ingredient in the drug cocktail fen-phen. The complementary nature of phentermine suggests a smaller increase in utilization after the withdrawal of Redux and Pondimin than one would predict if phentermine were exclusively a substitute for the withdrawn drugs. Markets in which remaining drugs are exclusively substitutes may exhibit greater competitive benefits and weaker negative spillovers.

Third, the withdrawn IBS drug Lotronex is a special case because it was returned to market in November of 2002, approved for only a small segment of the patient population. There is no respondent in the 2002 MEPS data who reports taking Lotronex, but the fact that it was returned to market at all makes it a special case and may limit its generalization to permanent drug withdrawals in other classes.

Conclusions

Our findings complement a literature in finance that documents changes in the prices of shares in pharmaceutical companies after a rival firm's drug is withdrawn from the market. Some papers in that literature document negative spillovers (Jarrell and

Peltzman, 1985) while others document competitive benefits (e.g. Ahmed et al., 2002; Dowdell et al. 1992). Our results vary by drug class. For three classes (obesity, pain, and IBS) we find evidence of negative spillovers, while in two others (heartburn and cholesterol) we find evidence of competitive benefits. In another class (hypertension) we find evidence of both negative spillovers (in the form of decreased utilization and initiations) and competitive benefits (in the form of lower quits). Across all drug classes and outcomes, the evidence for competitive benefits is weaker because it is also consistent with trends in unobserved factors or idiosyncratic comparison years.

These results also have implications for drug product market definition. Both the positive and negative spillovers in the wake of drug withdrawal we document suggest that drugs within the same therapeutic class are to some extent substitutable and hence compete within the same product market. Finally, our paper also relates to a recent literature in pharmaceutical economics that documents consumer responses to positive information such as direct-to-consumer advertising (Rosenthal et al. 2003; Iizuka and Jin 2003). Our finding establishes that the effects of bad news also can spill over throughout a drug class.

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Table 1
Seven Drug Withdrawals Studied

Brand Name of Withdrawn Drug	Indication Treated	Date Withdrawn	Primary Health Risk (Reason Drug Withdrawn)	Name of Class	Drugs In Class Remaining on Market
Pondimin Redux	Obesity	9/15/1997	Valvular heart disease	Anorectics	Adipex, Ionamin, Meridia, Phentermine, Diethylpropion, Dexedrine
Duract	Pain	6/22/1998	Liver failure	Non-steroidal anti-inflammatory	Arthrotec, Naproxon, Ibuprofin, Diclofenac, Daypro, Diclofenac Sodium
Posicor	Hypertension	6/8/1998	Lowered heart rate, adverse interactions with 26 other drugs	Calcium channel blockers	Adalat, Calan, Cardizem, Covera, Diltiazem Hcl, Norvasc
Propulsid	Heartburn	7/14/2000	Potentially fatal irregular heartbeat	GI stimulants	Metoclopramide Hcl, Reglan
Lotronex	Irritable Bowel Syndrome	11/28/2000	Ischemic colitis	Antidiarrheals	Carafate, Cytotec, Sucralfate
Baycol	High Cholesterol	8/8/2001	Fatal rhabdomyolysis	HMG-CoA Reductase Inhibitors	Lipitor, Zocor, Pravachol, Lescol, Mevacor

Table 2
Means of Dependent Variables
(Refer to *Non-Withdrawn* Drugs in Each Class)

Indication Treated by Class That Experienced Drug Withdrawal	Utilization	Initiations	Quits
Obesity	.005 (N=124,314)	.003 (N=55,030)	.665 (N=297)
Pain	.108 (N=124,314)	.065 (N=48,852)	.592 (N=6,475)
Hypertension	.068 (N=124,314)	.015 (N=51,730)	.230 (N=3,597)
Heartburn	.004 (N=124,314)	.002 (N=55,125)	.549 (N=202)
IBS	.004 (N=124,314)	.002 (N=55,133)	.632 (N=194)
Cholesterol	.065 (N=124,314)	.022 (N=51,926)	.148 (N=3,401)

Notes:
1) Data: Medical Expenditure Panel Survey, 1996-2002
2) Each row refers to non-withdrawn drugs in a therapeutic class that remained after the named drugs were withdrawn. For example, the first row refers to obesity drugs that remained on the market after Redux and Pondimin were withdrawn.
3) Sample size shown in parentheses below mean of the dependent variable.

Table 3
Utilization of *non-withdrawn* drugs in that therapeutic class
N=124,314
Odds ratios and (t-statistics)

Indication Treated	*Withdrawal – 3 Years*	*Withdrawal – 2 Years*	*Year Withdrawn*	*Withdrawal + 1 Year*	*Withdrawal + 2 Years*	*Withdrawal + 3 Years*
Obesity			1.104	0.673**	0.664*	0.436***
			(0.70)	(2.16)	(1.93)	(4.18)
Pain		1.076*	0.960	0.886***	0.734***	0.684***
		(1.79)	(0.96)	(2.94)	(6.63)	(7.97)
Hypertension		1.291***	0.930	0.961	0.893*	0.892*
		(4.42)	(1.31)	(0.61)	(1.75)	(1.81)
Heartburn	0.598*	1.094	1.249	1.537**	1.408	
	(1.85)	(0.45)	(1.09)	(2.21)	(1.55)	
IBS	1.229	0.901	0.772	0.682*	0.919	
	(0.89)	(0.49)	(1.16)	(1.86)	(0.40)	
Cholesterol	0.781**	0.846**	1.271***	1.523***		
	(2.49)	(2.50)	(3.94)	(4.30)		

Notes:
1) Data: Medical Expenditure Panel Survey, 1996-2002
2) Cells contain odds ratios and the absolute value of t statistics in parentheses
3) Asterisks indicate statistical significance: * significant at 10%; ** significant at 5%; *** significant at 1%
4) In addition to time indicators, models control for the following regressors: the trend in per capita number of scrips in respondent's geographic area, indicator variables for whether the respondent has the condition treated by that class of drugs, gender, African-American, Hispanic, other race/ethnicity, married, whether the respondent has health insurance, whether the respondent's health insurance includes prescription drug coverage, age categories, urban residence, Census Region categories, income categories, and education categories.
5) Standard errors are cluster-corrected by individual
6) The STATA command svylogit is used to account for MEPS sample weights and the MEPS survey design (stratum and psu).

Table 4
Initiation of *non-withdrawn* drugs in that therapeutic class
Odds ratios and (t-statistics)

Indication Treated	*N*	*Withdrawal – 3 Years*	*Withdrawal – 2 Years*	*Year Withdrawn*	*Withdrawal + 1 Year*	*Withdrawal + 2 Years*	*Withdrawal + 3 Years*
Obesity	55,030				0.444***	0.506**	0.332***
					(2.68)	(2.07)	(3.82)
Pain	48,852			0.915	0.877*	0.703***	0.680***
				(1.14)	(1.89)	(4.12)	(4.46)
Hypertension	51,730			0.691**	0.888	0.894	0.994
				(2.30)	(0.66)	(0.74)	(0.04)
Heartburn	55,125	1.127	1.468	1.995	2.608**	1.330	
		(0.24)	(0.73)	(1.53)	(2.27)	(.059)	
IBS	55,133	1.175	0.720	0.607	0.458**	0.936	
		(0.43)	(0.97)	(1.16)	(2.09)	(0.16)	
Cholesterol	51,926	0.791	0.596***	0.905	1.269		
		(1.55)	(3.16)	(0.61)	(1.41)		

Notes:
1) Data: Medical Expenditure Panel Survey, 1996-2002
2) Cells contain odds ratios and the absolute value of t statistics in parentheses
3) Asterisks indicate statistical significance: * significant at 10%; ** significant at 5%; *** significant at 1%
4) In addition to time indicators, models control for the following regressors: the trend in per capita number of scrips in respondent's geographic area, indicator variables for whether the respondent has the condition treated by that class of drugs, gender, African-American, Hispanic, other race/ethnicity, married, whether the respondent has health insurance, whether the respondent's health insurance includes prescription drug coverage, age categories, urban residence, Census Region categories, income categories, and education categories.
5) Standard errors are cluster-corrected by individual
6) The STATA command svylogit is used to account for MEPS sample weights and the MEPS survey design (stratum and psu).

Table 5
Quits of *non-withdrawn* drugs in that therapeutic class
Odds ratios and (t-statistics)

Indication Treated	*N*	*Withdrawal – 3 Years*	*Withdrawal – 2 Years*	*Year Withdrawn*	*Withdrawal + 1 Year*	*Withdrawal + 2 Years*	*Withdrawal + 3 Years*
Obesity	297				2.133*	1.188	0.743
					(1.72)	(0.33)	(0.66)
Pain	6,475			0.871	1.066	1.134	1.242**
				(1.55)	(0.66)	(1.35)	(2.01)
Hypertension	3,597			0.603***	0.554***	0.613***	0.538***
				(3.38)	(3.53)	(3.30)	(3.66)
Heartburn	202	1.948	0.988	2.322	0.634	0.569	
		(0.97)	(0.02)	(1.31)	(0.74)	(0.83)	
IBS	194	1.508	0.533	1.305	1.763	3.233	
		(0.55)	(0.80)	(0.34)	(0.68)	(1.29)	
Cholesterol	3,400	0.665**	0.696*	0.717*	0.702*		
		(1.99)	(1.77)	(1.84)	(1.72)		

Notes:
1) Data: Medical Expenditure Panel Survey, 1996-2002
2) Cells contain odds ratios and the absolute value of t statistics in parentheses
3) Asterisks indicate statistical significance: * significant at 10%; ** significant at 5%; *** significant at 1%
4) In addition to time indicators, models control for the following regressors: the trend in per capita number of scrips in respondent's geographic area, indicator variables for whether the respondent has the condition treated by that class of drugs, gender, African-American, Hispanic, other race/ethnicity, married, whether the respondent has health insurance, whether the respondent's health insurance includes prescription drug coverage, age categories, urban residence, Census Region categories, income categories, and education categories.
5) Standard errors are cluster-corrected by individual