Short-termism, Bad News Disclosure, and Public Health

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Abstract

This paper studies whether capital market pressure has an impact on firms' real decisions, public health, and shareholders' wealth. Using data from the FDA Adverse Event Reporting System and Drug Recall Enforcement Reports for pharmaceutical firms, I examine whether short-term pressure influences the speed with which firms respond to adverse event reports through their recall decisions. Using duration analysis, I find that firms subject to greater short-term pressure exhibit significant delays in recalling drugs compared to firms under less pressure. This finding holds even when both types of firms are working on the same drug. I also find that 10% – 48% more adverse events were reported for firms under greater short-term pressure, indicating that more patients experienced adverse events due to delayed recalls. Furthermore, I document that delaying firms suffer from negative stock returns after recalls. The results suggest that capital market pressure affects the timing of bad news disclosure and firms' product recall decisions and highlights an important negative societal externality of managerial myopia.

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1 Introduction

This paper investigates whether short-term pressure influences firms' decisions regarding the timing of bad news disclosure, specifically through product recalls, and the potential repercussions on both public health and shareholders' wealth. Existing studies have shown that managers withhold bad news (e.g., Acharya, DeMarzo, and Kremer, 2011; Baginski, Campbell, Hinson, and Koo, 2018; Kothari, Shu, and Wysocki, 2009), and work for short-term profits even at the expense of long-term value creation (e.g., Graham, Harvey, and Rajgopal, 2005; Narayanan, 1985; Stein, 1989), particularly when their compensation depends on investor beliefs. Similarly, when facing short-term pressures, firms might be inclined to withhold information about newly identified risks associated with their products and delay initiating product recalls due to the short-term costs of recalls.

To examine this question, I consider the pharmaceutical industry because withholding product risks and delaying product recalls may have significant negative externalities on public health. To monitor the safety of marketed drugs and therapeutic biologic products, the Food and Drug Administration (FDA) designed the FDA Adverse Event Reporting System (FAERS). In 2021 alone, the FAERS recorded over 2.3 million adverse events, with approximately 188,000 of those cases resulting in patient deaths.[1] When serious adverse events related to a drug are reported to the FAERS, drug manufacturers have the opportunity to recall the drug, thereby preventing people from being further exposed to potentially

[1]According to the Centers for Disease Control and Prevention (CDC), the number of death cases due to adverse drug reactions each year is compatible with the number of deaths for leading causes in the U.S. Based on mortality in the United States (2018), the 10 leading causes of death in 2018 are: Heart disease (655,381), Cancer (599,274), Accidents (167,127), Chronic lower respiratory diseases (159,486), Stroke (147,810), Alzheimer's disease (122,019), Diabetes (84,946), Inuenza and Pneumonia (59,120), Nephritis, nephrotic syndrome and nephrosis (51,386), and Intentional self-harm (48,344).

harmful drugs. Even when a drug is not inherently defective, an early recall can protect public health by enabling firms to update the drug's labeling and prescribing information. By doing so, firms disclose newly identified risks and side effects to healthcare professionals and patients, facilitating their informed treatment decisions.

Although timely disclosure of product risks and preemptive recalls can enhance public health, firms would not voluntarily recall their drugs under short-term pressure before they find conclusive evidence that the drugs are defective for several reasons. First, recalls are costly. Kini, Shenoy, and Subramaniam (2017) estimate the costs of product recalls and show that the market value of a recalling company decreases by $256 million over the (-10, +10) days around the recall date on average. In addition, outsiders could mistakenly attribute bad short-term outcomes caused by factors beyond mangers' control to managerial incompetence as shown in Jenter and Kanaan (2015). Thus, a manager, who is compensated based on short-term performances and has career concern, would not recall a drug without solid evidence that the drug causes the adverse reactions. However, it is *ex ante* not clear whether this is the case. First, firms can reduce litigation costs by recalling drugs as soon as adverse event reports about their drugs are filed to the FAERS. In addition, publicly traded firms are subject to mandatory disclosure regulations, and they have to timely disclose material information. For these reasons, firms would recall their drugs and disclose the newly reported risks even without evidence that their drugs are harmful or defective.

One of the significant challenges in studying the timing of bad news disclosures is that it is hard for outsiders to discern whether a manager withholds bad news strategically or the manager does not have information to disclose (e.g., Dye, 1985). This study addresses this challenge by using the FAERS and Drug Recall Enforcement Reports database. As the

FAERS is publicly available, managers as well as outsiders can learn about the risks and side effects of drugs. Although an adverse event report itself does not establish a causal relationship between the drug and the adverse event, it alerts managers that the drug may have new risks and further adverse events may occur without taking preemptive actions. It is noteworthy that managers would be attentive to the FAERS because clinical reviewers actively monitor the database, and further investigation can be conducted if a potential safety concern is identified. Based on the evaluation results, the FDA may take regulatory actions, such as restricting the use of the drug, communicating new safety information to the public (Public Health Advisory), or, in rare cases, removing the product from the market. Thus, these databases enable me to examine whether short-term pressure plays a role in how quickly firms react to adverse event reports, given that outsiders know that managers are aware of the adverse events.

To investigate the effect of short-term pressure on the speed with which pharmaceutical firms respond to adverse event reports through drug recalls, I use a Cox proportional hazard model for the duration analysis. Following previous literature (e.g., Almeida, Fos, and Kronlund, 2016; Asker, Farre-Mensa, and Ljungqvist, 2015; Caskey and Ozel, 2017; Hribar, Jenkins, and Johnson, 2006), I measure the degree of short-term pressure at the firm-level based on (1) the frequency that the firm meets or beats the median analyst forecast by two cents or less, (2) the degree of ownership dispersion, and (3) the tendency that the firm conduct EPS-driven share repurchases when it would have narrowly missed the target without the repurchases. Then, I defined *short-term* firms as those that are in the top quartile (25th percentile) of each measure.

To rule out the possibility that the results are driven by unobserved drug characteristics,

I stratify the estimation within the drug in the main specification using the Cox regression. By doing so, I can investigate whether and the extent to which *short-term* firms delay recalls compared to *non-short-term* firms when those firms are working on the same drug. I also control for the number of adverse event reports and the severity of the adverse events. I find that *short-term* firms exhibit significant delays in recalling drugs relative to *non-short-term* firms. The results show that the likelihood that the drug will be recalled is 48% – 77.5% lower for *short-term* firms compared to *non-short-term* firms.

To corroborate the results, I conduct two additional tests. First, I drop the adverse event reports that were filed during the first 1.5 years in the sample period to address the possibility that the results are biased because of left-truncation of data. The left-truncation issue arises because adverse event reports filed before 2012 are not observable in the data. As a result, the initial adverse event report for a given drug-firm in the sample period of 2012 – 2017 may not be the first one. In addition, to rule out the possibility that the results are biased because of the noisy information in the FAERS database, I include observations in the sample only when there are more than five adverse event reports were filed for the drug-firm pair. I re-do the analyses for these two cases and find that the results are robust.

I also present evidence regarding the consequences of short-term pressure. First, I explore the impact of short-term pressure on public health by investigating the relationship between the number of adverse event reports and firm-level short-term pressure measures. After controlling for firm characteristics and time-invariant drug characteristics, I find that more adverse event reports were filed for drugs produced by *short-term* firms. Following previous literature (Caskey and Ozel, 2017; Cohn and Wardlaw, 2016), I use count models, such as Poisson and Negative Binomial models, to address concerns about the skewed distribution

of the number of adverse event reports and find that the results are similar. Taking more time to recall a drug does not necessarily lead to a higher likelihood of experiencing adverse events because consumers can make well-informed treatment decisions with proper disclosure of risks and side effects of the drug (e.g., through a timely update of prescribing information). However, the findings suggest that more people experienced adverse events during the sample period because firms withhold the important safety information by delaying recalls under short-term pressure.

Further, I investigate whether the delayed recalls are penalized by the market. To examine this possibility, I construct quintile portfolios based on the time from the initial adverse event report dates to recall initiation dates and compare the recalling firms' buy-and-hold abnormal returns (BHARs) over the market portfolio across the portfolios. I find that the differences in BHARs for early recalling firms (Q1) and delaying firms (Q5) are statistically and economically significant. The differences in BHAR[0,30] and BHAR[0,60] between Q1 and Q5 are 7.01% and 13.12%, respectively. The severe stock market penalty for delaying firms suggests that recall costs become greater as recalls are delayed.

This paper contributes to several strands of literature. First, this paper contributes to the literature on the timing of bad news disclosure (Acharya et al., 2011; Bertomeu, Ma, and Marinovic, 2020; deHaan, Shevlin, and Thornock, 2015; Johnson and So, 2018; Tse and Tucker, 2010; Ma, Marinovic, and Karaca-Mandic, 2015) and the effects of short-termism on firms' real decisions (Almeida et al., 2016; Asker et al., 2015; Bereskin, Hsu, and Rotenberg, 2018; Terry, 2022). The evidence provided in this paper shows that firms under greater short-term pressure tend to withhold information regarding serious product risks and safety issues for longer periods of time after adverse event reports were filed by delaying product

recalls.

In addition, this paper contributes to the literature on the costs and externalities of short-term pressure (Caskey and Ozel, 2017; Edmans, Fang, and Huang, 2022; Eilert, Jayachandran, Kalaignanam, and Swartz, 2017; Liu, Shen, Welker, Zhang, and Zhao, 2021; Raghunandan, 2021) by presenting evidence that short-term pressure inflicts harm not only on shareholders' wealth but also on public health. Instead of promptly updating prescribing information and disclosing newly found safety issues and risks through the recall process as soon as they become aware of adverse events regarding their products to facilitate informed decisions for healthcare professionals and consumers, firms under short-term pressure tend to delay product recalls. The results suggest that people experience serious adverse events, including death, hospitalization, and life-threatening situations, among others, due to the delayed product recalls and risk disclosures by firms under short-term pressure.

The rest of the paper is organized as follows. Section 2 reviews the related literature and develops hypotheses. Section 3 presents the sample construction process and research design. Section 4 contains the results, and Section 5 concludes.

2 Institutional background

2.1 FDA Adverse Event Reports

Approximately 2.2 million hospitalized patients in the U.S. experience adverse drug reactions, and 106,000 of those patients had fatal ones in 1994 (Lazarou, Pomeranz, and Corey, 1998). The FDA Adverse Event Reporting System (FAERS) was designed to monitor the

safety of marketed drugs and therapeutic products. The FAERS database contains information on adverse event reports, medication errors, and product quality complaints that have been submitted to the FDA. Reports submitted to the FAERS come from various sources, including healthcare professionals, consumers, and manufacturers. Healthcare professionals, such as physicians, pharmacists, and nurses, along with consumers, including patients, family members, and legal representatives, can voluntarily submit reports directly to the FDA. Additionally, healthcare professionals and consumers can report adverse events to the product manufacturers, who are then required by regulations to forward the reports to the FDA.

The FAERS plays a vital role in various FDA activities, including the identification of potential safety concerns associated with marketed products, assessing manufacturers' compliance with reporting regulations, and responding to external requests for information. Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) outlines the FDA's responsibility to "conduct regular, bi-weekly screening of the Adverse Event Reporting System [AERS] database." As a result, clinical reviewers at the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) carefully analyze the reports in the FAERS to monitor the safety of post-marketed products approved by the FDA. Whenever a possible safety issue emerges from the FAERS data, a comprehensive evaluation follows.[2] When a significant safety issue with the potential to alter the benefit-risk analysis of a drug is identified, the FDA can implement regulatory actions to enhance product safety and protect public health. These actions could

[2] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system

include updating a product's labeling information, restricting its use, disseminating new safety information to the public, or, in rare cases, removing the product from the market.

2.2 Drug Recalls and Disclosing Risks and Safety Information

When the FAERS identifies a serious risk or safety information, a drug recall is one of the most efficient methods to protect the public from a faulty or potentially harmful product. The FDA plays a crucial role in this process by supervising the firm's approach, categorizing its severity, and evaluating the recall's effectiveness.[3] The FDA classifies recalls into one of the following categories based on the degree of risk involved:

- Class I: A dangerous or defective product that could cause serious health problems or death.
- Class II: A product that might cause a temporary health problem, or pose slight threat of a serious nature.
- Class II: A product that might cause a temporary health problem, or pose slight threat of a serious nature.

In most cases, Class I recall notifications include patient instructions detailing the necessary actions to be taken. The FDA assesses the recall's effectiveness through the firm's notification process and the successful removal of the defective product from the market. In cases where the recall is deemed ineffective, the FDA will ask the company to implement further corrective measures.

The FDA also plays a crucial role in communicating potential post-marketing drug safety issues to the public. The FDAAA directs the FDA to post "any new safety information or

[3] https://www.fda.gov/drugs/drug-recalls/fdas-role-drug-recalls

potential signal of a serious risk identified by the Adverse Event Reporting System" on the FAERS website. The FDA notes that when new safety information is reported in the FAERS, it does not imply that the FDA has concluded the drugs are defective or directly responsible for the adverse events. The FDA emphasizes that healthcare providers can continue to prescribe the drug while the potential risk is being evaluated. However, disclosing information about newly found safety issues for a drug is crucially important. This early disclosure helps facilitate informed treatment decisions for both medical professionals and patients, even in the absence of evidence that establishes a direct causal relationship between the drug and the adverse event.

In addition to the role of the FDA, it involves a voluntary effort by a pharmaceutical firm to withdraw a defective drug from the market and to disclose potential safety information to the public. For example, Bristol-Myer Squibb, one of the world's largest pharmaceutical companies, voluntarily recalled Eliquis (Active Ingredient: Apixaban), a drug developed jointly by Bristol-Myers Squibb and Pfizer to prevent blood clots and stroke, in 2017 as a precautionary measure based on a single customer complaint about a mislabeled bottle.[4] However, it appears that Bristol-Myer Squibb was reluctant to disclose the risk of its product. The FDA posted on the FAERS website that the prescribing information for Eliquis was updated in April 2021, incorporating a description of the newly identified risk.[5] It may not be considered a timely action given the severeness and amount of adverse events. During

[4]A bottle labeled as Eliquis 5 mg was found to contain Eliquis 2.5 mg tablets (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/update-voluntary-recall-eliquisr-apixaban-5-mg-tablets-hn0063-recall-retaildispensing-level-only)

[5]In Appendix A and B, both labels are presented, showing the original label before the revision and the updated label after the revision. The comparison aims to highlight the changes made to the label content based on the newly identified safety issues and risks associated with the drug. (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/january-march-2021-potential-signals-serious-risksnew-safety-information-identified-fda-adverse)

the period from January 2013 to March 2021, a total of 71,563 adverse events were reported regarding Eliquis. Among these, 47,277 patients experienced serious adverse outcomes, including 10,620 deaths and 15,876 hospitalizations.

3 Related literature and hypothesis development

As noted in Kanodia and Sapra (2016), corporate myopia is a pervasive problem. Narayanan (1985) shows concern that managers are "working for short-term profits at the expense of the long-term interests of their firms." In their survey study, Graham et al. (2005) note that "80% of survey participants [CFOs] report that they would decrease discretionary spending on R&D, advertising, and maintenance to meet an earnings target" and more than half "would delay starting a new project to meet an earnings target, even if such a delay entailed a small sacrifice in value." Previous studies provide evidence of the effect short-termism on long-term returns (Edmans et al., 2022), R&D investment (Terry, 2022), employee wage (Raghunandan, 2021), and work place safety (Caskey and Ozel, 2017).

Prior literature attributes the short-term bias of corporate managers to liquid and disbursed ownership of stock market listed firms (Bhide, 1993), compensation schemes that contingent on short-term performances, such as stock price or EPS (Hribar et al., 2006; Lazonick, 2014; Stein, 1989), and managers' career concern (Baginski et al., 2018) among others. Regardless of the source of the short-term pressure, it is important to understand whether short-term pressure affects managers' decisions and, if so, whether and to what extent it entails externalities.

It is noteworthy that information asymmetry between managers and outside investors

allows managers to distort decisions (e.g., R&D) for short-term profits at the expense of long-term profits (e.g., Narayanan, 1985). For example, von Thadden (1995) shows that subobtimal investment problems due to corporate myopia cannot be solved without active monitoring activities by investors. Consistently, previous studies document that managers can withhold bad news for their private benefits when investors do not know the managers' information endowment (e.g., Acharya et al., 2011; Baginski et al., 2018; Kothari et al., 2009). In contrast, if the market knows that a manager is informed, then the manager will disclose its information in equilibrium because in the absence of disclosure, investors may assume the worst scenario (Grossman, 1981; Milgrom, 1981).

In the setting of this study, information asymmetry may still exist between pharmaceutical firm managers and outsiders, even though adverse event reports are publicly observable through the FAERS because it is not easy to access the FAERS data without knowledge of database application such as MySQL and SAS analytic tools. People can send a Freedom of Information Act (FOIA) to FDA to receive the reports, but users can only get a summary report or individual case report. This information asymmetry allows pharmaceutical firm managers to delay costly drug recalls under short-term pressure.

I predict that firms are likely to delay recall decisions under short-term pressure because the recalling firms suffer from the decrease in sales, negative stock market reactions, and reputational costs (e.g., Dranove and Olsen, 1994; Kini et al., 2017). Therefore, as featured in Stein (1989), capital market pressure may induce the manager to withhold information regarding the risk of the product and delay costly recall decisions to make the firm look good in the eyes of investors in the short-term, even though it may not be desirable for the long-term interest of the firm. Specifically, I argue that firms under greater short-term

pressure are slower in recalling drugs after adverse event reports about their drugs are filed to the FAERS relative to firms under less pressure because managers who care short-term performances would not voluntarily recall their drugs until they find conclusive evidence that the drugs are defective or have dangerous side effects indeed.

However, there are several reasons why this may not be the case. First, firms can mitigate litigation risks and reduce recall costs by taking actions early before more people experience adverse events (e.g., Freund, Nguyen, and Phan, 2022; Shaout and Dusute, 2014). In addition, publicly traded firms are subject to mandatory disclosure regulations and have to timely and faithfully disclose material information. Skinner (1994) notes that managers may incur reputational costs for withholding bad news. Further, as in Acharya et al. (2011), adverse event reports filed to the FAERS may trigger the manufacturer's prompt disclosure of accurate safety information about drug before consumers are exposed to negative sentiments and misinformation (Yousefinaghani, Dara, Mubareka, Papadopoulos, and Sharif, 2021). Therefore, it is an empirical question whether withholding product defects and delaying recalls are more prevalent in firms under greater short-term pressure than in firms under lesser pressure. This leads to the following hypothesis:

H1 (null): There is no impact of short-term pressure on the speed with which firms recall drugs after adverse event reports about their drugs were filed to the FAERS.

4 Data and Research Design

4.1 Data and Sample

The starting point for the construction of my drug-firm level sample is the FAERS database. From the FAERS, I download and parse adverse event report data filed between January 2012 and September 2017. Then I merge the FAERS data with the Drug Recall Enforcement Reports database based on drug and manufacturer information. Figure 1 shows the number of adverse event reports filed to the FAERS by the seriousness of the events. According to the FAERS, 'serious' events include hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome. Between January 2012 and September 2017, more than 8.4 million adverse events were reported, and of these, 4.3 million and 810,000 reports involve 'serious' and 'death' cases, respectively. However, this should be interpreted with caution because the information in the FAERS may not be reliable since it has not been medically confirmed as the FDA noted. It is possible that the underlying diseases being treated by the drug or another drug that the patient is taking concurrently could cause the event.

That said, the utilization of the FAERS and the Drug Recall Enforcement Reports database enables me to investigate the influence of short-term pressure on managers' decisions concerning the timing of drug recalls. Although not everyone may have direct access to the precise date of the first adverse event report for a specific drug without expertise in database applications, it is still possible to observe when a manager becomes aware of the safety issue through the FAERS. Using the merged data, for a given drug i produced by firm j, I calculate the number of days between the first adverse event report filing date and the re-

call initiation date. I focus on drugs that produced by more than two firms because the time until recall may vary depending on idiosyncratic drug characteristics. This approach allows me to examine whether short-term pressure influences the speed with which firms, working on the same drug, respond to the adverse event reports through their recall decisions.

To measure short-term pressure and control for firm characteristics, I obtain firms' financial data from Compustat, analyst EPS forecast data from I/B/E/S, stock-related data from CRSP, and institutional ownership data from Refinitiv Institutional 13f Holdings. Following previous literature (Caskey and Ozel, 2017; Raghunandan, 2021; Liu et al., 2021; Hribar et al., 2006; Almeida et al., 2016; Lazonick, 2014), I measure short-term pressure at the firm-level as (1) the frequency that the firm meets or beats the median analyst forecast by two cents or less (*Suspect*), (2) the degree of ownership dispersion (*InstOwn*)[6], and (3) the tendency that the firm conduct EPS-driven share repurchases when it would have narrowly missed the target without the repurchases (*AccRep*)[7]. Then, I defined short-term firms as those that are in the top quartile (25th percentile) of each measure.

4.2 Research Design

I use a Cox proportional hazard model to examine the effect of short-term pressure on how fast firms respond to adverse event reports through recall decisions. The hazard rate of recall represents the probability that a drug is recalled at time t given that the drug has not been recalled until $t-1$. For the duration analysis, I set the duration as the spell of time until

[6]Dispersed investors cannot effectively evaluate complex operations and long-term investments.

[7]*AccRep* is an accretive share repurchase that increases EPS by at least one cent, conducted when a firm would have narrowly missed the target without the repurchase. Previous studies show that firms strategically use stock repurchases to meet short-term targets, when they would have narrowly missed the targets without the repurchases.

recall, measured as the number of days between the date when the first adverse report was filed to the FAERS and the recall initiation date for any given drug-firm pairs.

$$h_{ij}(t) = h_{0i}(t) \times exp[\beta_1 ShortTerm_j + \beta_2 ln(\#AER)_{ij} + \beta_3 Serious_{ij} + \gamma X'_j] \quad (1)$$

where $h_{ij}(t)$ is the hazard rate of recall at time t for drug i and firm j, conditional on survival until t, and $h_0(t) =$ is the baseline hazard rate of recall, $\#AER_{ij}$ is the number of adverse event reports, *Serious* is the average severeness of adverse events, X are control variables including firm characteristics such as Size, Net Income, R&D, Market-to-Book, Leverage, and Capital Expenditure. To rule out the possibility that recall decisions are determined by unobserved drug characteristics, I stratify the baseline hazard rate by drugs and examine the effect of short-term pressure on recall timing within drugs.

5 Results

5.1 Timing of drug recalls

In this section, I present the results of this study. First, I report the cumulative hazard estimates for *short-term* and *non-short-term* firms. Table 2 and Figures 3, 4, and 5 show that at any given time between 25 and 1,929 days from the initial adverse event report date, drug produced by *short-term* firms are less likely to be recalled compared to drugs produced by *non-short-term* firms.

In the main specification, I include size, net income, R&D expenditure, market-to-book ratio, leverage, and capital expenditure to control for time-varying firm characteristics that

may affect the timing of drug recalls after receiving adverse event reports. In addition, I stratify estimations within drug to rule out the possibility that unobserved drug characteristics drive the results. Using a sample period of 2012 – 2017, I find that *short-term* firms exhibit significant delays in recalling drugs relative to *non-short-term* firms. The hazard ratio of 0.225 – 0.520 for *short-term* firms indicates that conditional on the drug has not been recalled until today, the likelihood that the drug will be recalled tomorrow is 48% – 77.5% lower for short-term firms holding constant the number of adverse event reports and the average seriousness of those reports.

To corroborate the results, I conduct sets of robustness tests. First, to rule out the possibility that the results are biased because of left truncation of data, I drop the adverse event reports filed in the first 1.5 years in the sample period. The left truncation issue arises because the initial adverse event report for a given drug-firm in the sample period of 2012 – 2017 may not be the first one because here could be an adverse event report filed even before 2012. In the analysis excluding adverse event reports filed in the first 1.5 years in the sample period, I find that the results are similar, suggesting that the results are not biased by left truncation (Panel A in Table 4). Also, as the FAERS database could contain noisy information, I use drug-firm observations only if more than five adverse event reports were filed. Then I rerun the Cox regressions and confirm that the results are similar (Panel B in Table 4).

5.2 Consequences of delayed recalls

I also investigate whether short-term pressure has negative externality on public health. To examine this possibility, I regress the number of AERs on firm-level short-term pressure measures using the following empirical model:

$$\#AERs_{ij} = \beta_1 ShortTerm_j + \beta_2 Serious_{ij} + \gamma X_j' + \theta_i + \epsilon_{ij} \tag{2}$$

where drug fixed effects are represented by θ_i.

After controlling for firm characteristics and time-invariant drug characteristics, I find that more AERs were filed for each drug for short-term firms (Panel A in Table 5). To address concerns about the skewed distribution of the number of AERs (Figure 2), I use count models following previous literature (Cohn and Wardlaw, 2016; Caskey and Ozel, 2017). Estimates from the poisson and negative binomial model show that about 10% – 48% more AERs per drug were filed for *short-term* firms relative to *non-short-term* firms (Panel B and Panel C in Table 5). The results indicate that more people experienced adverse events, involving death, hospitalization, life-threatening, or other serious outcomes during the sample period due to the delayed recalls.

I further investigate the effect of short-term pressure on stock performance. I construct a quintile portfolio based on the number of days from the initial AER filing date to the recall date, then compare the recalling firms' buy-and-hold abnormal returns (BHARs) over the value-weighted market portfolio across the time-to-recall portfolios. I first confirm that there is no significant difference between Q1 (the fastest recalls) and Q5 (the most delayed recalls) portfolios before recall dates (BHAR[-60,-1] and BHAR[-30,-1]). However, I find

that the differences become significant after the event dates. The differences in BHAR[0,30] and BHAR[0,60] between Q1 and Q5 are 7.01% and 13.12%, respectively. I also investigate whether delayed recalls affect the long-term stock performances. Using monthly return data, I find that the market penalty for delayed recalls are most severe in the first 12 months, then diminish over time. I find that the difference in monthly returns between Q1 and Q5 portfolios becomes insignificant after 36 months from the recall dates. I confirm that the results are similar when using BHARs over the equal-weighted market return. The severe stock market penalty for delaying firms suggests that recall costs become greater as recalls are delayed (e.g., the greater number of drugs to be recalled, the higher litigation costs).

6 Conclusion

In this paper, I examine whether capital market pressure influences managers' real decisions and has impacts on public health, and shareholders' wealth. Specifically, I investigate whether short-term pressure affects how fast firms respond to adverse event reports through their recall decisions. To do so, I construct the unique data based on the FDA Adverse Event Reporting System and Drug Recall Enforcement Reports. I use duration analysis and find that firms under greater short-term pressure exhibit significant delays in recalling drugs, withholding important product risks, relative to firms under less pressure. The results hold after controlling for various firm and drug characteristics. In addition, I document that more people are experience adverse events due to the delayed recalls and delaying firms suffer from severe negative stock returns after the recall dates. The findings of this study highlight the real effects and an important negative externality of managerial myopia.

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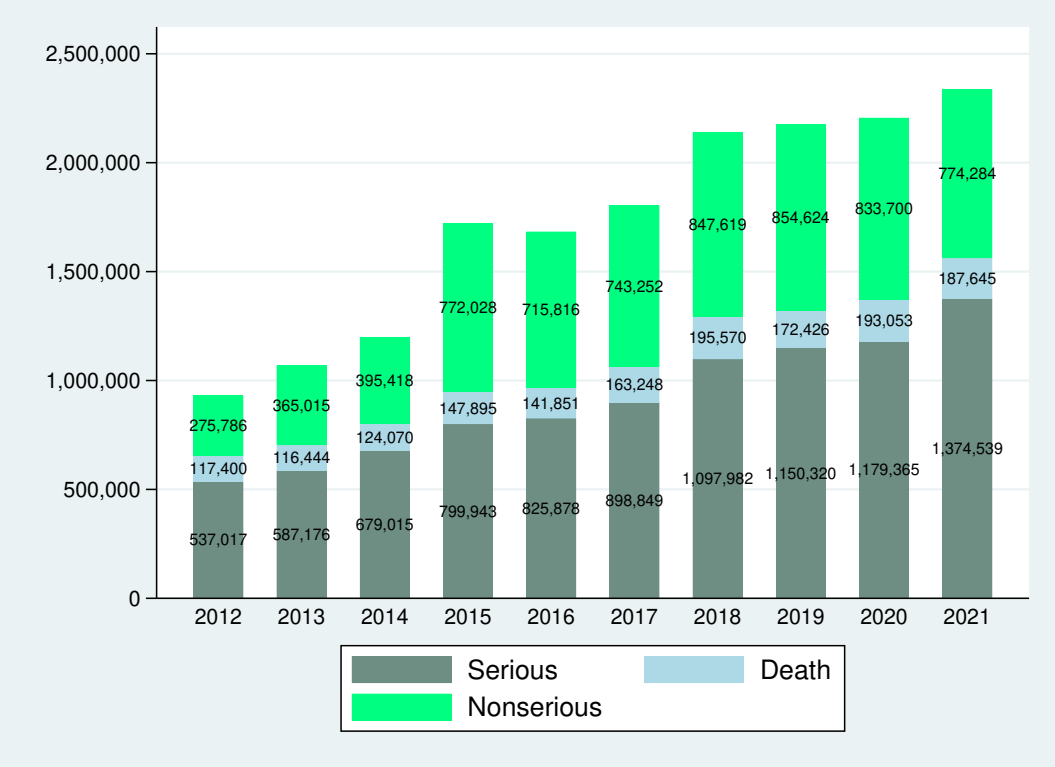

Figure 1. Adverse Event Reports by Seriousness

This figure shows the number of adverse event reports by seriousness of the events from 2012 to 2021. "Serious" indicates that one or more of the following outcomes, excluding death, were documented in the report: hospitalization, life-threatening, disability, congenital anomaly, required intervention, and/or other serious outcome. "Death" indicates that the outcome was documented as Death. "Non-Serious" is used for outcomes which were not documented as Serious or Death.

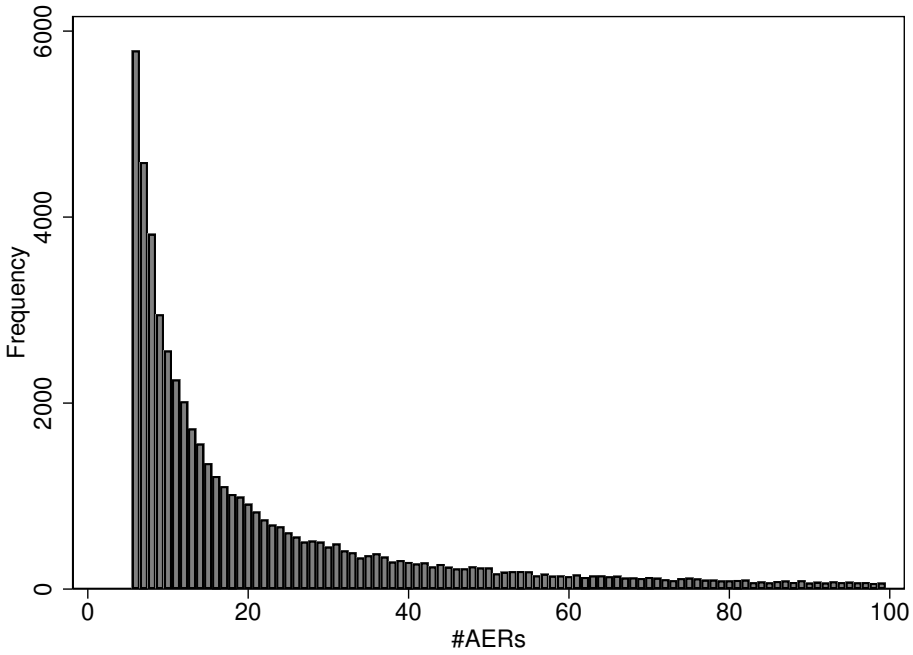

Figure 2

This figure presents a histogram showing the distribution of the number of adverse event reports.

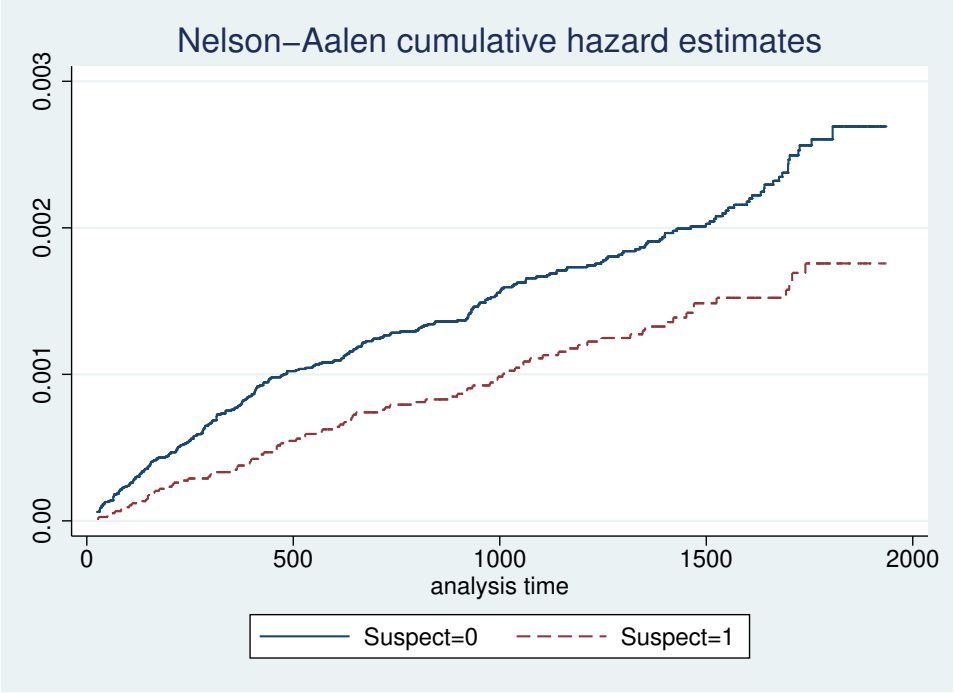

Figure 3

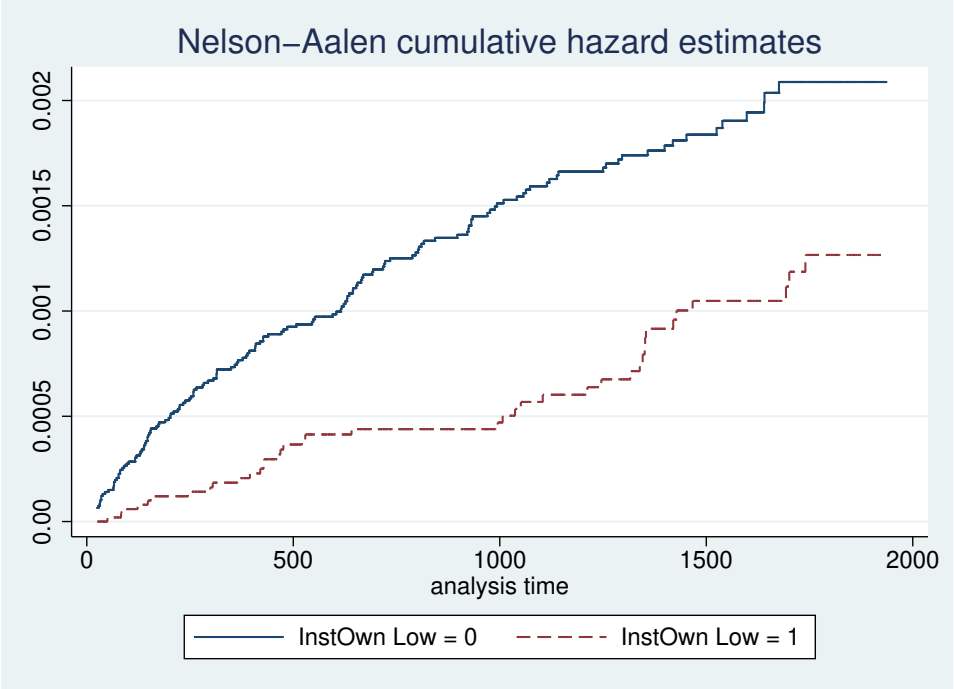

Figure 4

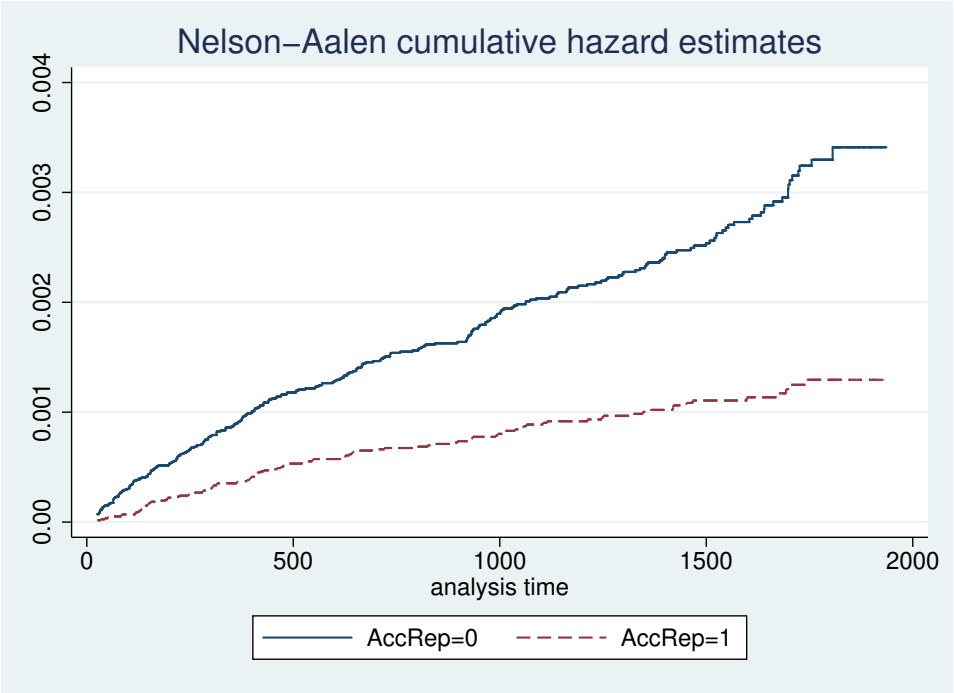

Figure 5

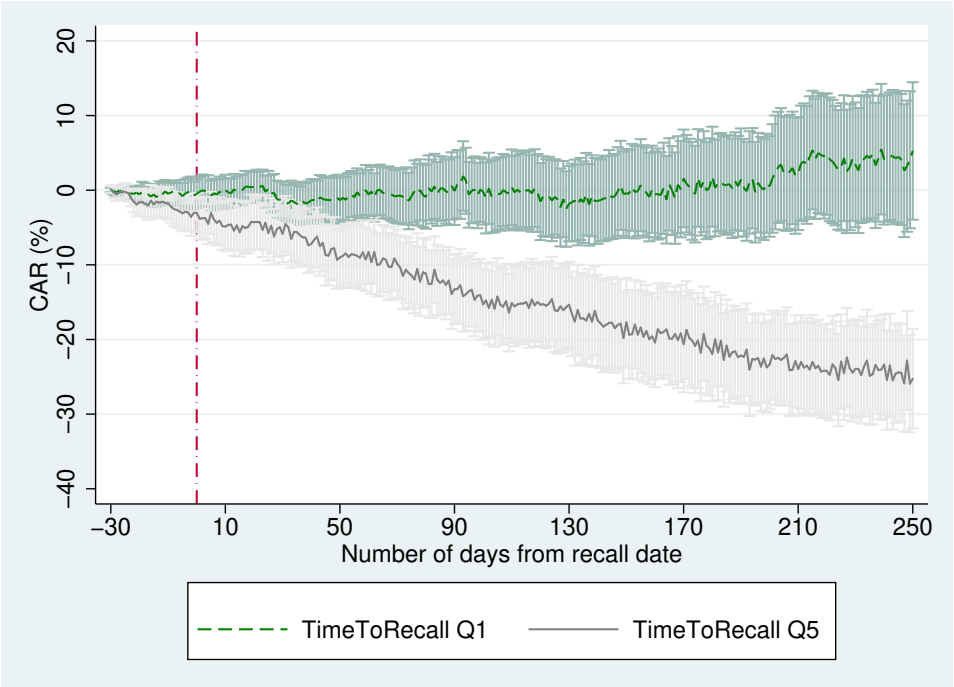

Figure 6. Buy-and-hold abnormal returns (BHARs) for Q1 and Q5 portfolios

Table 1
Summary Statistics

	N	Mean	p25	Median	p75
FAERS					
#AERs	255,307	33.442	1.000	2.000	5.000
Short-term pressure					
#Suspect	255,307	2.794	1.000	3.000	4.000
InstOwn (%)	159,253	0.288	0.225	0.268	0.333
#AccRep	255,307	5.884	0.000	4.000	11.00
Controls					
SIZE	255,307	9.810	8.542	10.554	11.26
NI	255,060	0.004	-0.001	0.014	0.024
R&D	255,307	0.026	0.010	0.018	0.027
MKB	254,446	2.952	1.758	2.124	3.103
LEV	250,234	0.330	0.214	0.285	0.450
CAPX	255,271	0.012	0.004	0.008	0.014

#AERs is the number of adverse event reports for drug i produced by firm j. #Suspect is the frequency that the firm meets or beats the median analysts forecast by two cents or less. InstOwn is the percentage of shares held by Top 5 institutional investors. #AccRep is the number of accretive repurchases aggregated at the firm level. As in Almeida et al. (2016), share repurchases are measured as the increase in the firm's common treasury stock. If both current and previous year's common treasury stocks are zero or missing, I calculate the difference between the stock purchased and the stock sold. If these amounts are negative or missing, I set share repurchase as zero. SIZE is natural logarithm of total assets. NI is net income scaled by total assets. R&D is R&D expenses scaled by total assets. MKB is market-to-book ratio. LEV leverage ratio, defined as total debt divided by total assets. CAPX is capital expenditures scaled by total assets.

Table 2

Nelson-Aalen cumulative hazard function

	Suspect		InstOwn Low		AccRep	
Time	= 0	= 1	= 0	= 1	= 0	= 1
25	0.0001	0.0000	0.0001	0.0000	0.0001	0.0000
263	0.0006	0.0003	0.0006	0.0001	0.0007	0.0003
501	0.0010	0.0005	0.0009	0.0004	0.0012	0.0005
739	0.0013	0.0007	0.0013	0.0004	0.0015	0.0007
977	0.0016	0.0009	0.0015	0.0004	0.0018	0.0008
1215	0.0018	0.0011	0.0017	0.0006	0.0022	0.0009
1453	0.0020	0.0013	0.0018	0.0010	0.0025	0.0011
1691	0.0024	0.0014	0.0021	0.0010	0.0030	0.0012
1929	0.0028	0.0016	0.0021	0.0013	0.0034	0.0013

Time is the number of days between the date when the first adverse event report was filed to FAERS and the recall initiation date for any given drug-firm pairs. *Suspect* is an indicator equal to one if the frequency that the firm meets or beats the median analysts forecast by two cents or less, aggregated at the firm-level (*#Suspect*) is in the top quartile. *InstOwn Low* is an indicator equal to one if the percent of shares held by largest 5 institutional investors (*InstOwn*) is in the bottom quartile. AccRep is an indicator equal to one if the number of accretive repurchases aggregated at the firm level (*#AccRep*) is in the top quartile.

Table 3

Cox regression

	Hazard Ratio		
	(1)	(2)	(3)
Suspect	0.520***		
	(-4.30)		
InstOwn Low		0.347***	
		(-5.70)	
AccRep			0.225***
			(-11.07)
AER	2.014***	1.940***	2.196***
	(20.52)	(11.53)	(20.21)
SERIOUS	1.343	0.864	1.533**
	(1.63)	(-0.52)	(2.29)
Controls	Y	Y	Y
Observations	249,090	154,665	249,090

Suspect is an indicator equal to one if the frequency that the firm meets or beats the median analysts forecast by two cents or less, aggregated at the firm-level (*#Suspect*) is in the top quartile. *InstOwn Low* is an indicator equal to one if the percent of shares held by largest 5 institutional investors (*InstOwn*) is in the bottom quartile. AccRep is an indicator equal to one if the number of accretive repurchases aggregated at the firm level (*#AccRep*) is in the top quartile. *AER* is natural logarithm of the number of adverse event reports. *Serious* is the average severeness of adverse events. Estimation is stratified within drug. Standard errors are clustered at the drug-level. Results remain significant when standard errors are clustered at the drug-firm-level.

Table 4

Robustness Tests

Panel A: Cox regression - AERs from 2013Q3

	Hazard Ratio		
	(1)	(2)	(3)
Suspect	0.668**		
	(-2.65)		
InstOwn Low		0.441***	
		(-4.05)	
AccRep			0.259***
			(-9.69)
AER	2.042***	1.938***	2.184***
	(18.77)	(10.92)	(18.75)
Serious	1.101	0.712	1.152
	(0.48)	(-1.19)	(0.69)
Controls	Y	Y	Y
Observations	232,274	142,580	232,274

Panel B: Cox regression - #AERs > 5

	Hazard Ratio		
	(1)	(2)	(3)
Suspect	0.573***		
	(-3.26)		
InstOwn Low		0.340***	
		(-5.13)	
AccRep			0.256***
			(-9.35)
AER	1.947***	1.949***	2.105***
	(14.83)	(8.81)	(14.60)
Serious	1.276	0.840	1.484
	(1.16)	(-0.56)	(1.77)
Controls	Y	Y	Y
Observations	59,783	36,981	59,783

Suspect is an indicator equal to one if the frequency that the firm meets or beats the median analysts forecast by two cents or less, aggregated at the firm-level (*#Suspect*) is in the top quartile. *InstOwn Low* is an indicator equal to one if the percent of shares held by largest 5 institutional investors (*InstOwn*) is in the bottom quartile. AccRep is an indicator equal to one if the number of accretive repurchases aggregated at the firm level (*#AccRep*) is in the top quartile. *AER* is natural logarithm of the number of adverse event reports. *Serious* is the average severeness of adverse events. Estimation is stratified within drug. Standard errors are clustered at the drug-level. Results remain significant when standard errors are clustered at the drug-firm-level.

Table 5

Effects of short-term pressure on public health

Panel A: OLS

	(1) #AERs	(2) #AERs	(3) #AERs
Suspect	5.418***		
	(18.92)		
InstOwn Low		10.384***	
		(26.24)	
AccRep			11.061***
			(27.75)
Controls	Y	Y	Y
Drug FE	Y	Y	Y
Observations	218,049	131,343	218,049

Panel B: Poisson

	(1) #AERs	(2) #AERs	(3) #AERs
Suspect	0.123***		
	(11.95)		
InstOwn Low		0.235***	
		(16.94)	
AccRep			0.393***
			(33.92)
Controls	Y	Y	Y
Drug FE	Y	Y	Y
Observations	218,049	131,343	218,049

Panel C: Negative Binomial model

	(1) #AERs	(2) #AERs	(3) #AERs
Suspect	0.095***		
	(22.17)		
InstOwn Low		0.168***	
		(31.35)	
AccRep			0.160***
			(38.46)
Controls	Y	Y	Y
Drug FE	Y	Y	Y
Observations	218,049	131,343	218,049

#AERs is the number of adverse event reports for drug i produced by firm j. *Suspect* is an indicator equal to one if the frequency that the firm meets or beats the median analysts forecast by two cents or less, aggregated at the firm-level (*#Suspect*) is in the top quartile. *InstOwn Low* is an indicator equal to one if the percent of shares held by largest 5 institutional investors (*InstOwn*) is in the bottom quartile. AccRep is an indicator equal to one if the number of accretive repurchases aggregated at the firm level (*#AccRep*) is in the top quartile. *AER* is natural logarithm of the number of adverse event reports. Standard errors are clustered at the drug level for OLS and Poisson.

Table 6
Time To Recall Portfolios

Portfolios	Average Time to Recall (days)	Number of Recalls
Q1	76	77
Q2	247	76
Q3	469	76
Q4	854	76
Q5	1416	76

Table 7

BHAR over market portfolio by Time To Recall Quintiles

Panel A: Value-weighted market return

	Time To Recall						
	Q1	Q2	Q3	Q4	Q5	Q1-Q5	t-stat
Daily return							
BHAR [-60,-1]	0.731	2.888	7.553	-0.826	-3.984	4.715	1.229
BHAR [-30,-1]	-0.582	0.860	4.770	0.820	-1.221	0.639	0.217
BHAR [0,30]	2.025	3.285	2.290	0.476	-4.988	7.013**	2.199
BHAR [0,60]	3.313	8.210	3.453	1.812	-9.810	13.123**	2.513
Monthly return							
BHAR [0,12]	35.070	52.968	37.610	41.531	-14.869	49.939**	2.103
BHAR [13,24]	11.133	13.071	-2.823	-18.048	-25.736	36.869***	4.535
BHAR [25,36]	-3.537	-28.226	-24.254	-21.546	-24.359	20.821**	2.309
BHAR [37,48]	-8.765	-31.261	-41.036	-20.832	5.043	-13.807	-0.957

Panel B: Equal-weighted market return

	Time To Recall						
	Q1	Q2	Q3	Q4	Q5	Q1-Q5	t-stat
Daily return							
BHAR [-60,-1]	1.215	2.247	6.621	0.775	-5.088	6.303	1.641
BHAR [-30,-1]	-0.106	0.770	4.001	1.887	-2.906	2.800	1.035
BHAR [0,30]	2.258	3.493	3.346	0.894	-4.880	7.138**	2.293
BHAR [0,60]	3.732	7.847	4.908	2.269	-9.219	12.951**	2.444
Monthly return							
BHAR [0,12]	37.493	60.661	47.416	47.231	-5.495	42.988*	1.756
BHAR [13,24]	19.677	21.811	5.732	-11.118	-10.187	29.864***	4.177
BHAR [25,36]	4.603	-25.869	-20.160	-11.827	-10.759	15.363*	1.668
BHAR [37,48]	-10.246	-24.274	-48.385	-18.320	-15.549	5.303	0.369

This table contains the buy-and-hold abnormal return (BHAR) across *TimeToRecall* portfolios, where BHAR[x,y] denotes the cumulative market-adjusted return from day x to y relative to the drug recall initiation date.

Appendix A. Prescribing Information for Eliquis - Before the revision

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS (apixaban) tablets for oral use
Initial U.S. Approval: 2012

WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

See full prescribing information for complete boxed warning.

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered. (2.4, 5.1)

----------INDICATIONS AND USAGE----------

ELIQUIS is a factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose is 5 mg orally twice daily. (2.1)
- In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 2.5 mg and 5 mg (3)

----------CONTRAINDICATIONS----------

- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (4)

----------WARNINGS AND PRECAUTIONS----------

- ELIQUIS can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban: Reduce ELIQUIS dose to 2.5 mg or avoid concomitant use. (2.2, 7.1, 12.3)
- Simultaneous use of strong inducers of CYP3A4 and P-gp reduces blood levels of apixaban: Avoid concomitant use. (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- *Nursing Mothers:* Discontinue drug or discontinue nursing. (8.3)
- *Pregnancy:* Not recommended. (8.1)
- *Severe Hepatic Impairment:* Not recommended. (12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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7.2 Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3)]*.

7.3 Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.77%/year with apixaban versus 0.62%/year with placebo in patients receiving single antiplatelet therapy and was 5.91%/year with apixaban versus 2.50%/year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4,

and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

8.2 Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions (5.2)]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

8.3 Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total subjects in clinical studies of apixaban, >69% were 65 and older, and >31% were 75 and older. The effects of ELIQUIS on the risk of stroke and major bleeding compared to warfarin were maintained in geriatric subjects.

Appendix B. Prescribing Information for Eliquis - After the revision

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS® (apixaban) tablets, for oral use
Initial U.S. Approval: 2012

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS
(B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.4, 5.1, 14.1)
(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.3)

----------INDICATIONS AND USAGE----------
ELIQUIS is a factor Xa inhibitor indicated:
- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. (1.2)
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5)

----------DOSAGE AND ADMINISTRATION----------
- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.1)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)
- Treatment of DVT and PE:
  - The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
- Reduction in the risk of recurrent DVT and PE following initial therapy:
  - The recommended dose is 2.5 mg taken orally twice daily. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 2.5 mg and 5 mg (3)

----------CONTRAINDICATIONS----------
- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (4)

----------WARNINGS AND PRECAUTIONS----------
- ELIQUIS can cause serious, potentially fatal, bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of apixaban is available. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.4)
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome: ELIQUIS use not recommended. (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban. Reduce ELIQUIS dose or avoid coadministration. (2.5, 7.1, 12.3)
- Simultaneous use of combined P-gp and strong CYP3A4 inducers reduces blood levels of apixaban: Avoid concomitant use. (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Not recommended. (8.1)
- *Lactation:* Discontinue drug or discontinue nursing. (8.2)
- *Severe Hepatic Impairment:* Not recommended. (8.7, 12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS *[see Clinical Pharmacology (12.3)]*.

7.2 Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3)]*.

7.3 Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of ELIQUIS in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with ELIQUIS compared to placebo. The rate of ISTH major bleeding was 2.8% per year with ELIQUIS versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with ELIQUIS versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery. In animal reproduction studies, no adverse developmental effects were seen when apixaban was administered to rats (orally), rabbits (intravenously) and mice (orally) during organogenesis at unbound apixaban exposure levels up to 4, 1 and 19 times, respectively, the human exposure based on area under plasma-concentration time curve (AUC) at the Maximum Recommended Human Dose (MRHD) of 5 mg twice daily.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk of thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reactions

Use of anticoagulants, including ELIQUIS, may increase the risk of bleeding in the fetus and neonate.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions (5.3)]*.

Data

Animal Data

No developmental toxicities were observed when apixaban was administered during organogenesis to rats (orally), rabbits (intravenously) and mice (orally) at unbound apixaban exposure levels 4, 1, and 19 times, respectively, the human exposures at the MRHD. There was no evidence of fetal bleeding, although conceptus exposure was confirmed in rats and rabbits. Oral administration of apixaban to rat dams from gestation day 6 through lactation day 21 at maternal unbound apixaban exposures ranging from 1.4 to 5 times the human exposures at the MRHD was not associated with reduced maternal mortality or reduced conceptus/neonatal viability, although increased incidences of peri-vaginal bleeding were observed in dams at all doses. There was no evidence of neonatal bleeding.

8.2 Lactation

Risk Summary

There are no data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Apixaban and/or its metabolites were present in